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ANNALS OF INTERNAL MEDICINE

VOLUME 14 JANUARY, 1941 NUMBER 7

THE SIGNIFICANCE OF URINARY pH: CRITICAL OBSERVATIONS *

By MILTON A. BRIDGES, M.D., F.A.C.P.,† and MARJORIE R. MATTICE, M.S., *New York, N. Y.*

IT would appear to be unnecessary to discuss so simple a matter as urinary reaction but the average clinician not infrequently is puzzled by apparent inconsistencies and opinions which are expressed as fact. Although reaction can be interpreted as titratable acidity with or without additional data, present comments will be restricted almost entirely to reaction as measured by pH.

NORMAL URINARY REACTION

Henderson and Palmer [1] reported a normal range of urinary pH of 4.82 to 7.45 with a mean of 6.03. Later [2] a value of 8.7 was achieved after administration of excessive amounts of sodium bicarbonate and pH 4.7 was found to occur in the presence of a trace of free phosphoric acid. In collaboration with Newburgh [3] they observed that normal subjects averaged pH 6; less than 1 per cent reached an acidity greater than pH 5.0 and less than 10 per cent pH 5.3 on 24-hour specimens. In 1914 Henderson and Palmer [4] obtained an average of 5.98 on 222 cases, the normal being regarded as pH 6 ± 0.1. Maslow,[5] testing 24-hour specimens preserved with toluene, averaged pH 6.02 with a range of 5.1 to 6.8 on 141 adults.

Fischer [6] citing Höber (1906) reported normal morning urine to vary from pH 5.3 to 5.5 (data calculated from cH) in 5 cases. Bowman and Pitts [7] on catheterizing hospital patients without pyelitis observed a range of pH 4.6 to 7.6 on morning urine. Lloyd-Williams [8] regarded pH 5.5 to 8.0 as the "symptomless zone" although he noted that pH 5 to 7 usually was the accepted normal range.

Marshall [9] states that human urine probably never becomes more alka-

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line than pH 8, this value being reached only under therapy. The maximum urinary concentration of sodium bicarbonate is about 0.22 molar and is supposedly not exceeded even when the body has occasion to rid itself of greater amounts of this base.[10]

In our experience, values on normal individuals fluctuate throughout the day about pH 6, the extreme limits of oscillation being 4.6 and 8.0. These values are given for room temperature. Correction to 38° C. necessitates subtraction of approximately 0.2 pH from observations made at 25° C.

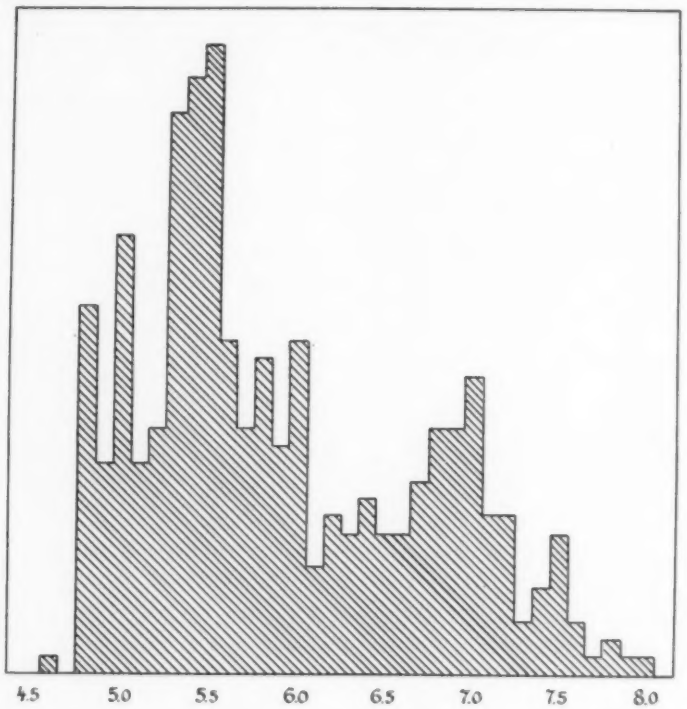

FIG. 1. Frequency distribution of 417 urine specimens on the same individual.

Figure 1 demonstrates the frequency distribution of 417 urine samples on a single individual. These were not specimens collected at random but represent every voiding for periods as extensive as two weeks at a time. Reactions below pH 6 account for 251 (60 per cent) of the specimens. Only 59 (11.7 per cent) reached pH 7 or higher. Although these observations include short intervals in which acidic-ash and alkaline-ash diets were followed, a mixed diet was the customary routine. The tests were conducted in summer when a plentiful variety of fresh fruits and vegetables was available. Although the protein intake was better than average, the amount of meat and fish consumed was moderate. These data were assembled under conditions which, from a nutritional standpoint, would be

considered wholly satisfactory. The tests were completed within 30 seconds of voiding, the subject serving as analyst.

The surprising degree of acidity noted might not be duplicated, however, under similar circumstances if the specimens were spaced further apart. In many instances very small volumes (5 to 30 ml.) were obtained for the specific purpose of ascertaining how rapidly the reaction might undergo change. In particular, the effect of ingesting food was studied and it was found that the *immediate* response to a meal was a change in the direction of greater acidity.[11] The reaction often varied by as much as two pH units in voidings less than 30 minutes apart.

From investigations reported elsewhere [11] it may be concluded that there is no single value for urinary pH which may be regarded as normal. Normality is characterized by variability. Furthermore, the daily fluctuations tend to form a pattern which is typical of the individual. These fluctuations constitute an acid-base tide the effect of which usually is manifest in the presence of incidental or experimental factors which also influence urinary reaction. In brief, it is not possible to correlate in any simple fashion the reaction of a single urine specimen with physiologic behavior or with experimental conditions.

Pathologic Urinary Reaction

If it is difficult to define any one value as the normal pH of urine, it is doubly so in pathologic states. Henderson and Palmer [1] reported pH 5.33 as the mean for "cardio-renal disease." These same investigators, together with Newburgh,[3] observed in cardiac decompensation pH values of 4.7 to 5.3 (average 4.9) on 24-hour specimens. Höber (1906) cited by Fischer [6] encountered in a few cases of nephritis morning urine of pH 4.6 to 5.3 (data calculated from cH), the greatest acidity being seen in the acute forms with diminished fluid output, much albumin and many casts. Ziegler and Brice [12] found that the majority of cases showed alkaline urine in fatal uremia.

Lloyd-Williams [8] presents some very startling values for urinary pH, such as 3.3 and 3.8 in elderly persons whose only complaint apparently was "frequency of micturition and scalding." The same symptoms were reported in a child whose urine was pH 8.7, no sediment being present. This investigator states that "in febrile conditions a figure of 4.2 can easily be reached." These results are far beyond anything we have ever seen.

Fixation of Urinary Reaction. If definite variation of urinary reaction is the normal behavior, fixation is to be regarded with apprehension. Although "fixation of pH" may be sufficient for clinical purposes, these logarithmic values correspond to different grades of acidity with change in position on the pH scale and, therefore, cannot be readily compared. Even the term *average pH* may be somewhat absurd under strict interpretation. The authors have used a system which permits a numerical evaluation of

urinary variation in reaction by converting pH values into "acid activity" units.[13] Preliminary observations have shown that the *difference* between the highest and lowest reading on a series of 8 to 10 urine specimens voided during 24 hours normally reaches 50 "acid activity" units or points. In our opinion, the extent and frequency of urinary change in reaction are a measure of renal efficiency. No method has been found which will "force" the excretion of highly acid urine for contrast with a strongly alkaline specimen within fixed time. In other words, it has been impossible either by administration of drugs or by dietary manipulation to shift the urine reaction deliberately from one extreme to the other.

In mild nephritis we have encountered differences of 20 to 30 "points" whereas in terminal nephritis the difference has been less than 1. A case of bacterial endocarditis (fatal) was characterized by extremely acid urine with variations from pH 4.7 to 5.0 which correspond to an "acid activity" difference of 100. Such observations, however, require confirmation from further clinical experience.

Anomalies of Urinary Reaction. The reaction of the urine is no dependable indication of the existence of acidosis or alkalosis. With *normal kidney function,* both the ingestion of acid-producing or acidifying drugs and the accumulation of ketonic acids due to metabolic disturbances will result in the excretion of unusual amounts of acid. After several days of excessive acid intake, however, the urinary pH will rise in spite of continued acid ingestion. Furthermore, ketonuria is not necessarily associated with acid urine. Ziegler and Brice[12] noted six alkaline specimens which contained a trace of acetone. They regarded this finding as rather unusual and not understood. Schrader[15] is cited as having reported the same phenomenon. Such cases have been seen repeatedly in this laboratory.

Although not an every-day occurrence, it is not unusual for the "admission urine" of surgical patients to be neutral or alkaline in the presence of traces or small amounts of acetone. We have noted this particularly with cases scheduled for surgery involving the alimentary tract, as carcinoma of the mouth, appendectomy, perianal abscess, and hemorrhoids. These findings are such as might be expected since the apprehension which escorts many surgical patients to the hospital is not conducive to renal efficiency, the consequence being diminished excretion of acid.[11] Concurrently, the nutritional status of these patients is generally unsatisfactory, as reflected by the urinary ketones.

In loss of fluids through vomiting, ketogenesis ensues unless glucose in adequate amounts is introduced into the body. These ketones appear in the urine regardless of its reaction. Furthermore, the administration of large doses of sodium bicarbonate to normal persons experimentally or to others therapeutically so affects the oxidation of glucose that ketonic acids result from faulty combustion of the fats, in which case appreciable amounts of $NaHCO_3$ and ketones are excreted simultaneously. It should be stressed

that "acetone breath" and ketonuria are usually but not invariably associated with acidosis.

Acid Urine in Alkalosis. In preserving the *total* electrolyte content of plasma the kidneys ordinarily distinguish between sodium and potassium, chloride and bicarbonate, but they will allow the normal ratios of these radicals to undergo drastic alteration if the total base is low. When this occurs, the kidneys will not excrete bicarbonate although definite alkalosis (relative excess of plasma sodium bicarbonate) exists. Likewise, no alkaline urine results from overventilation if the body can ill afford to throw away base. Also, prompt excretion of ingested water does not occur since its removal entails loss of at least some base.

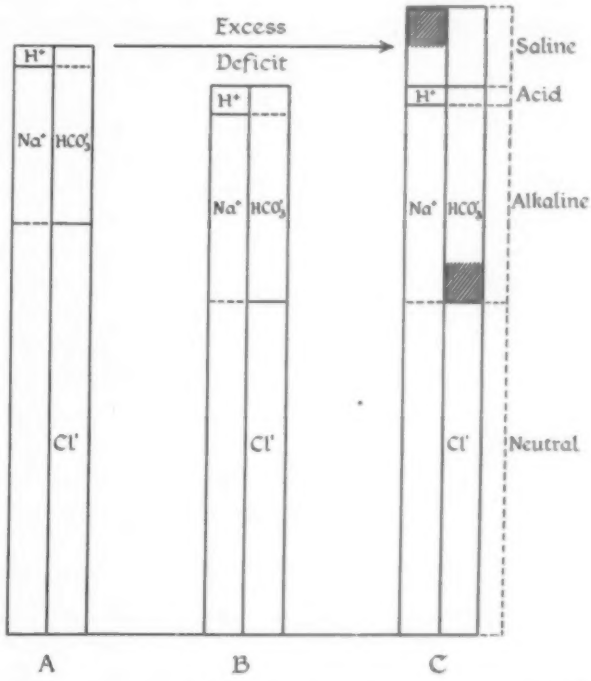

FIG. 2. Diagrammatic representation of the relationship between the chief electrolytes of the plasma.

In the blood plasma, Na^+ is balanced by varying amounts of HCO_3^- and Cl^-. As is well known, the $NaHCO_3$ is alkaline in reaction whereas the NaCl is neutral. A small amount of H^+ is balanced by HCO_3^- and is, of course, acid. For ease in representation, figure 2 has not been made proportional to the actual normal ratios ($Cl : HCO_3 :: 4 : 1$, and $NaHCO_3 : H_2CO_3 :: 20 : 1$, both suitably expressed). In pyloric obstruction, for instance, there is greater loss of Cl^- than Na^+, together with marked dehydration. The consequence is a drop in the total Na^+ in the plasma but a relative increase in the bicarbonate which replaces part of the lost chloride—a base

deficit with increased alkalinity (figure 2B). Were the kidneys to excrete some of the $NaHCO_3$ to restore the ratio of bicarbonate to chloride, the sodium would be reduced to an intolerable level. Despite the presence of alkalosis, such urine as is excreted is acid, first because it allows greater concentration of waste products [12] and second, because it conserves body base. When, however, saline is administered, both water and base become available. Sodium is excreted until the electrolyte level is normal; it carries with it the unwanted HCO_3^-, thus producing an alkaline (or at least less acid) urine (figure 2C).

Nicol [16] has pointed out that the kidneys quickly compensate for alkalemia unaccompanied by dehydration, but severe vomiting followed by dehydration results in a toxic nephritis as evidenced by albuminuria and the appearance of casts and red blood cells in the urinary sediment, the urine remaining acid despite the alkalemia. Nicol observed that correction of the dehydration with sodium chloride brought about the disappearance of the albumin, cells and casts and the excretion of an alkaline urine so long as the plasma CO_2 C.P. remained elevated. It was concluded that dehydration results in oliguria which produces tubular damage (as shown by postmortem findings) so hampering the excretion of alkali.

Unsuspected cases of alkalosis have been encountered among both diabetics and nephritics. One such, a patient with diabetes, arteriosclerosis and chronic myocarditis was admitted for treatment of a carbuncle. Analysis of the blood showed: sugar 288 mg. per cent, CO_2 C.P. 75.8 volumes per cent, and pH 7.6. The urine was acid and contained 0.28 per cent sugar as well as two plus acetone and diacetic acid. At the time there was no explanation for the alkalosis.

Way and Muntwyler [17] reported cases of renal disease showing relatively little nitrogen retention but marked elevation of blood pressure. Both pH and CO_2 C.P. were increased and chlorides lowered. Despite the blood alkalinity, the urine remained acid, often strongly so. With progression of the renal disability, acidosis ensued.

Myers and Booher [18] reported two cases where strongly acid urine was noted in the presence of alkalosis due to administration of sodium bicarbonate. Issue was taken with Palmer [19] who contended that sufficient check on the therapeutic use of this drug was obtained by testing the urine until it reached pH 7, at which time the bicarbonate was to be discontinued. Myers did not believe that the urine reaction was a safe guide since some individuals with apparently normal kidneys fail to excrete alkali readily. This belief has been borne out by repeated observations in this same laboratory; unfortunately, they have not been committed to the literature.

Alkaline Urine in Nephritic Acidosis. With progressive failure in renal function, elaboration of a concentrated acid urine becomes impossible. The fixation of pH at lower levels, which is seen in earlier nephritis, gradually shifts in the direction of neutrality. Death often ensues when the pH level reaches 6.5 to 6.8, the turning point of litmus. Where routine

urine is tested with litmus paper, it is reported as alkaline while still below pH 7. Added to this that urine of low specific gravity contains few buffer substances and readily changes its reaction to definite alkalinity on standing, it can be seen that the urine will frequently be "alkaline" despite the fact that these patients are acidotic.

Experimentally, Stieglitz [20] has observed that the secretion of an alkaline urine leaves the tubular cells acid, whereas increasing alkalinity of the cells results when acid urine is secreted. In nephritis this reciprocal relationship is altered, the injured cells remaining acid and the urine likewise. This does not necessarily imply, however, that the urine is strongly acid in all stages of nephritis as is commonly supposed.

Alteration of Urinary Reaction

The urine reaction is amenable to change under certain conditions. No intelligent procedure can be outlined for specific application without a knowledge of the characteristics of the individual's acid-base curve.[11] Attack then can be directed against those points where the reaction is other than that desired, just as is done in apportioning the insulin dosage of the diabetic. For example, a daily curve which shows an "alkaline" specimen late in the forenoon with definite acidity holding throughout the remainder of the day can be flattened by selection of suitable foods or drugs a few hours earlier. Such a subject, however, would be difficult to alkalinize except with large doses of sodium bicarbonate. Similarly, a person whose only acid specimen was obtained on arising would resist fixation of the urine at pH 5. Alkalinization of this morning urine could be achieved only by medication at night, the wisdom of such a procedure being questionable.

Factors Affecting Urinary Reaction. In actual practice it will be found that the response of patients to acidification or alkalinization measures is highly variable and conditioned by manifold factors including such intangible ones as emotional states. Summarizing our experience with considerable hesitation, the primary tendency of various individual factors which influence urinary pH appears to be as follows:

Personality: In sthenic types, there is greater acidity, greater variability, and fixation is less readily achieved.

Water Excretion: Unless counteracted by other forces, increase in water output raises the pH. Water retention at night usually is associated with increased acidity. Loss of water through vomiting, diarrhea, catharsis, and sweating increases urinary acidity.

Emotional Status: Polyuria of nervous origin is associated with increased pH. Tense attitudes which diminish water excretion increase acidity. Apprehension may diminish the output of acid. Petty annoyance is apt to raise the pH. Working under pressure may lead to fixation at alkaline or acid levels despite diuresis. Sthenic individuals under pleasurable emotional stimulus tend toward greater acidity.

Meals: Ingestion of food more often than not is associated with immediate increase in acidity followed by changes dependent upon the composition of the food and related to the time of day.

Rate of Ventilation: Overventilation leads to diminished acidity if water and base are available for excretion.

Exercise: Diminished water output occurs together with increased acidity.

Fatigue: Where mental processes are involved, the pH rises.

Pathologic States: Edema formation is associated with greater acidity, discharge of edema with rising pH. Diabetic acidosis generally is accompanied by marked acidity unless ammonia excretion is high. There is fixation of urinary pH at unusually low levels in cardio-renal disease. In terminal nephritis neutrality is encountered. Those anomalies associated with loss of fluid through the alimentary tract have been discussed elsewhere at some length.

The observed urinary pH is always the resultant of several factors operating at one and the same time. These generalizations, then, will be helpful only as they are correlated and checked by the experience of others.

Means of Changing Urinary Reaction. The extent of urinary pH change desired, naturally, affects the selection of method for its alteration. There are many instances in the practice of medicine where general indisposition or specific complaints can be met with an altered dietary regimen. Those with a predilection for alkaline-ash foods will derive benefit from acid-producing foods, and vice versa. When changes in reaction are contemplated, it should be remembered that forcing fluids tends to raise the urinary pH while withholding water lowers it.

The ketogenic diet is not well tolerated by the majority who require definite acidification. The use of acidic-ash foods is more effective in the long run. As ordinarily applied, such a diet not infrequently fails to lower the urinary pH below 5.5. This is due not only to the characteristics of the individual's natural pH curve, but also to lack of strictness in arranging the diet. The absence of salad and cooked greens in particular may be annoying to the patient. These greens may be allowed once daily if ample amounts of cranberry, plum or prune juices are taken to the exclusion of other fluids. Where it is deemed advisable, lactic acid milk may be employed in lieu of the fruit juices suggested. Ice cream is permissible on both acidic and alkaline-ash diets.

Crance and Maloney[21] in a preliminary report advised a regular diet acidified with 10-minim doses of concentrated nitrohydrochloric acid (18 parts HNO_3 to 82 parts HCl) after meals and late at night. At least one glass of water is taken with each dose. The use of hydrochloric acid, either alone or in conjunction with nitric acid, has been ineffective in lowering the pH to the neighborhood of 5 in our experience[11] whereas the benzoic and quinic acid fruits have easily accomplished this. It seems paradoxical, but it can be verified in practice, that withdrawal of hydrochloric acid medication

is followed by increase in urinary acidity, the diet remaining unaltered. This is occasioned by the fact that the elimination of water taken with the acid nullifies its effect inasmuch as the increased urinary volume results in an upward trend in the pH. Could the nitrohydrochloric acid be administered with less water it would be more effective.

The more common drugs for acidifying urine include sodium acid phosphate (average dose 10 to 30 gr.), sodium benzoate (average dose 15 to 30 gr.), ammonium chloride (average dose 15 gr., in amounts up to 120 gr. daily) and ammonium nitrate (dosage as for ammonium chloride). Ammonium or monoethanolamine mandelate (10 to 15 gr. in amounts up to 180 gr. daily) is employed for acidification and for its bactericidal effect. When used in conjunction with ammonium chloride, 10 gr. of the former and 7 gr. of the latter are usually given t.i.d.

On alkaline-ash diets the withdrawal of cereal products may constitute a hardship in which case two slices of bread daily may be allowed. Unless contra-indicated, an egg should be included every day except where the diet is of short duration. The melons, bananas, pears and apples are particularly well suited to raising urinary pH.[11] In preliminary experiments Shohl's citrate solution [22] has proved to be useful where it has been impractical to alter the basic diet. This consists of 20 ml. of molar citric acid (210 gm. $H_3C_6H_5O_7 . H_2O$ per liter) plus 30 ml. of molar citrate (294 gm. $Na_3C_6H_5O_7 . 2H_2O$ per liter). Although the pH of the mixture is not unduly acid, the citrate is so concentrated as to require dilution of 5 to 10 times for ingestion. Milk can be used as a vehicle although water is usually more convenient. As dictated by the natural acid-base rhythm of the patient and the response to the citrate, the dose is administered as a whole or divided. In accordance with individual preference it can be taken before, after or during meals.

The use of this citrate can be illustrated with a case that showed pH 6.4, 6.8, 6.5, 7.1 and 7.0 during the period from 11:30 a.m. (when 50 ml. of citrate were taken) to 10:45 p.m. The same patient on the same basic mixed diet with the exception that cranberry juice was taken over the same time interval presented a lowering of urinary pH to 5.8, 5.6, 6.2, 5.9 and 5.5. This patient was not particularly prompt in the removal of either base or acid. A demonstrably normal subject reached pH 7.6 two hours after ingesting the citrate. Five hours later, despite the excretion of only 150 ml. in this interval, the urinary pH was 7.2. Cranberry juice (125 ml. with an equal amount of water) produced a pH of 5.0 and 5.3 respectively on precisely the same water output (360 ml.).

McClellan and Goldstein [23] compared urinary pH after the ingestion of plain and mineral waters which contained 2 to 5 gm. of the bicarbonate and carbonates of sodium, calcium, and magnesium per liter. When 500 or 1,000 ml. of mineral water were included with breakfast, the subsequent urinary reaction varied between pH 6.5 and 8.0 throughout the 24 hours. The greater the diuresis the more nearly the pH approached 7. The shift

into the alkaline range was directly proportional to the alkaline content of the different mineral waters used. To maintain continuously alkaline urine, 45 gm. of sodium bicarbonate may be required daily.[24]

Reasons for Changing Urinary Reaction. To quote from Mason and Hellbaum[25]: "Many physicians make a routine practice of prescribing alkalies, and also alkali diet, in the treatment of nephritis. They usually do so with no better reason than 'if it does not benefit the patient, it can at least do no harm.' Also the general public has been 'sold' on the idea that all human ills result from a 'too acid' condition, and the panacea is alkali. Berger and Binger[26] have observed impaired renal function accompanying alkalosis, resulting from the alkaline treatment of peptic ulcer. Steele[27] has also observed that renal damage may occur in the alkaline ulcer treatment before clinical symptoms of alkalosis appear. . . . Ziegler and Brice[12] warned against the indiscriminate use of alkalies, as alkalinization of the urine may defeat the purpose, which is elimination of solids."

On the other hand,[25] "we have no evidence that prolonged use of an acid salt has an injurious effect on the kidney. Very recently Noth has reported the treatment of a case of Pick's disease in which 6 grams of ammonium nitrate were administered daily for over three years with no evidence of hepatic or renal damage."

Ziegler and Brice[12] found the acid type of therapy superior to the alkaline in managing nephritis. Mason and Hellbaum,[25] as well as others, have discovered that Lashmet's[28] treatment of nephritic edema "works." Essentially it consists of a low-protein, salt-poor, neutral-ash diet in conjunction with acid-producing salts and "forced" fluids.

The influence of alkalies on renal function has received considerable attention from various investigators. The weight of opinion is against promiscuous use of alkaline therapy because of the tendency toward renal damage. As already pointed out[18] some persons with apparently normal kidneys do not eliminate alkali readily. Hardt and Rivers[29] were the first to describe toxic manifestations following alkaline treatment of duodenal ulcer where renal damage antedated the therapy and also where no such prior impairment existed. Shattuck, Rohdenburg, and Booher[30] also cited cases but noted that only a small group of ulcer patients receiving alkaline treatment were so affected.

In a short experimental study involving the use of calcium carbonate and magnesium oxide, McGee et al.[31] believed that they had evidence of a slight depression of renal function. Berger and Binger[26] presented an exceptional case with duodenal ulcer that for years "consumed pounds of both calcium carbonate and sodium bicarbonate every week" without apparent impairment of renal function.

It is believed that alkalinization should be attempted only with definite justification. Where extreme acidity is accompanied by frequency of micturition and a burning sensation, relief may be expected by inducing reac-

tions close to neutrality. There is no merit in achieving a continuously alkaline urine. It is of no benefit to the kidneys—rather the reverse. Since alkalinization of urine causes increasing renal cellular acidity as demonstrated by Stieglitz,[20] there is indeed no justification for producing this abnormal state. Later[32] applying experimental observations to the clinical paradox that diuresis may follow either alkali or acid therapy, Stieglitz suggested that the reversal of intracellular reaction produces physiologic irritation and thus renal diuresis by insult attributable to alkali whereas diuresis associated with the use of acids in nephritis probably results from some measure of physiologic neutralization of the renal secreting cells, thus improving their functional efficiency. Stieglitz has also shown that alkalinization of nephritic animals does not reverse the acid reaction of the injured kidney cells.

There arise occasions, however, when alkaline urine may be desirable. Hemoglobinuria subsequent to transfusion has been found by McGowin et al.[33] to be associated with renal impairment in dogs due to blockage of the tubular lumen with masses of pigment although the transfused blood was compatible. Partial or complete urine suppression occurred on acidic diets, but so long as the urine was alkaline intravenous injection of large amounts of dog hemoglobin appeared to be innocuous.

An acidic diet is dehydrating whereas marked and sudden gain in weight follows the administration of sodium bicarbonate.[25] Not only in edema but also in epilepsy and in obesity may advantage of this fact be taken. Subcaloric diets do not always lead to the expected loss in weight. Prompt elimination of water and consequent weight reduction are encountered with acid formation and a low salt intake.

Pitfalls in Urinary Fixation. It is one thing to alter the composition of urine so as to increase or decrease the excretion of acid or basic substances; it is quite another matter to attempt to hold the pH at a predetermined level. Apart from persistent ammoniacal fermentation in the bladder or the administration of large amounts of suitable drugs, it is impossible to secure consistently alkaline urine. Although acidification is more readily achieved than alkalinization, the initial low pH cannot be maintained indefinitely since metabolic adjustment is made for the increased ingestion of acidic substances if this is persisted in long enough to set in operation compensatory manufacture of ammonia. When the pH rises coincident with an increased output of ammonia regardless of the diet or further administration of acidifying drugs, the acid therapy should cease. Unless specifically contraindicated, a rational schedule calls for five days' acidification followed by two days of dietary relaxation in which the erstwhile forbidden foods and fluids are freely ingested. In particular, it is recommended that the Shohl citrate solution, previously mentioned, be employed in conjunction with a quart of milk daily.

On any acidification regimen, provision should be made for adequate intake of calcium. When cheese is tolerated, this item is invaluable. It

should be remembered that the rennet cheeses are ten times richer in calcium than those produced by acid coagulation. Since the acidic-ash diet is notably deficient in vitamin C, administration of ascorbic acid (50 mg. daily) is advised.

Continued acidification results in the loss of considerable calcium from the body. *Other circumstances permitting,* urinary calculi might be formed, in particular those composed of calcium oxalate. It is highly improbable that calculosis can be induced by altering the reaction of the urine, but prolonged fixation of pH might provoke crystallization under conditions conducive to stone formation. During acidification, therefore, the quantity and type of urinary deposit should be determined. The occurrence of a lateritious deposit should be viewed with apprehension and steps taken to decrease the need for the excretion of much uric acid.

It has been observed that urine as it leaves the ureteric orifices is already turbid in many vegetarians. It is recognized, of course, that ample supplies of cereals in the diet tend to off-set the alkalinity of vegetables and fruits. Neutral and alkaline urines, however, do not regularly exhibit the clarity of acid specimens but frequently show a copious deposit of phosphates. This turbidity, as a general occurrence, is most undesirable.

Summary

1. Normality of urine reaction is characterized by variability within the range of pH 4.6 to 8.0, lower values being observed much more frequently than higher ones.

2. Abnormality of urine reaction is characterized by fixation at levels typical of the disease.

3. Alkalosis (relative excess of plasma sodium bicarbonate) in conjunction with base deficit is associated with acid urine. The administration of adequate amounts of saline is followed by excretion of "alkaline" urine.

4. "Acetone breath" and ketonuria are usually associated with acidosis but will also occur in conditions covered by the term "alkalosis." Ketones may be found in abnormal amounts in urine of any reaction.

5. Elevated plasma pH and CO_2 C.P. together with acid urine may be encountered both in diabetes and renal disease.

6. The reaction of the urine is not a safe guide in the avoidance of alkalosis due to sodium bicarbonate therapy.

7. The acidosis of terminal nephritis is accompanied by urine close to neutrality in reaction, the blood and urine pH values moving toward each other.

8. The acid-base ratios of the tissues, blood and urine do not rise and fall concomitantly. The former possess compensating mechanisms in which the kidneys play an important rôle. Adjustment so secured of necessity requires the formation of urine of markedly different reaction from that within the body. Urinary pH per se, therefore, is of limited significance.

9. The response of patients to acidification or alkalinization is highly variable and conditioned by manifold factors including such intangible ones as emotional states. Some of these factors are mentioned.

10. The means of changing urine reaction and the reasons therefor are discussed.

11. The pitfalls encountered in acidifying or alkalinizing measures are cited.

12. Any arbitrary attempt to fix or shift urinary reaction in the direction of greater alkalinity should be regarded in the same light as alteration of gastric acidity—a matter undertaken only by the competent physician on cases presenting definite pathology and achieved by means which do not ignore the body's other needs. The daily removal of the acid end-products of metabolism is not a thing to be deplored and the urine promptly alkalinized. In so doing, the very purpose of urine formation may be defeated.[12]

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TREATMENT OF STAPHYLOCOCCAL SEPTICEMIA WITH SULFAMETHYLTHIAZOLE AND SULFATHIAZOLE; A REPORT OF TWELVE CASES*

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The reported mortality from staphylococcal septicemia associated with foci of all sorts varies from 8 to 90 per cent.[1-11] Inspection of the summary of recent reports in table 1 shows that though reduction in the general mortality has followed the use of one or another therapeutic agent, the invasion of the blood stream by staphylococci is still a grave matter. Moreover, strict criteria for diagnosis are not always defined. Stookey and Scarpellino[3] insisted upon the presence of three positive blood cultures for inclusion of cases in their series, and excluded all cases of osteomyelitis, but most authors have not laid down such rigid criteria. The presence of two positive blood cultures would seem to be a fair criterion in cases that are to constitute the basis of therapeutic evaluation, but in general, waiting for three positive cultures before beginning treatment is hardly justified.

Another gap in the armamentarium of evaluation is the lack of extensive data dealing with the mortality in bacteremic osteomyelitis. Stookey, Scarpellino, and Weaver[11] state, "Let it be recalled that in every case osteomyelitis is at its inception a bacteremia. The blood in a majority of cases eventually sterilizes itself, with the localization of the invading bacteria in certain bones." Robertson[12] said in 1938, "Some years ago, in studying cases of staphylococcal osteomyelitis, a routine examination of the blood for its bacterial count was made. If the culture was made a number of times, organisms were grown in every case." However, this statement is supported by neither a reference to the earlier work, nor by analytical statistical data. Despite these views, Baker and Shands[1] found that 70 per cent of 30 patients with bacteremic osteomyelitis died. It is generally agreed that osteomyelitis probably begins by transport of organisms to bone via the blood. May it not be, however, that the finding of bacteremia a week or more after the onset of symptoms represents a less favorable immunological situation, and accordingly a poorer prognosis than when the bacteria are recovered from the blood in the very beginning of the disease?

The evaluation of therapy in staphylococcal septicemia in general is more difficult than in pneumonia, for example, where case material is abundant, and alternate case studies can be made. Nevertheless, valuable data may accumulate by pooling reports from various clinics whose criteria

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of diagnosis are similar. It is the purpose of this communication to report our experience in the Cincinnati General Hospital with 27 cases of staphylococcal septicemia during the period 1933–39, and add 12 cases treated within the past year with thiazole derivatives of sulfanilamide.* Except as specifically indicated, all patients had at least two positive blood cultures. Our series includes all cases of staphylococcal septicemia, regardless of focus.

During the past year we have observed 12 patients treated with thiazole derivatives of sulfanilamide of whom eight have recovered. The four fatalities all occurred in patients with acute staphylococcal endocarditis. The distribution of the foci in the 12 cases was as follows: osteomyelitis, 3, of whom one had meningitis in addition; carbuncle, 2; gluteal abscess, 1; pyarthrosis, 1; fracture, 1; and endocarditis, 4.

Review of Previous Cases of Staphylococcal Sepsis at the Cincinnati General Hospital

In the files of the Cincinnati General Hospital from 1933 to 1939 are the records of 27 patients whose blood streams were invaded by the staphylococcus. Of this group, 20 had at least two positive blood cultures. Of the seven patients with only one positive culture, three died within 24 hours of admission to the hospital, and two patients had but one culture made. The other two patients with only one positive culture survived. There were but four recoveries in the entire group, a gross mortality of 85.2 per cent.

The fulminating character of staphylococcus septicemias has been recognized for a long time, and is borne out by the present series. The average total illness in the fatal cases was 17 days, with extremes of 4 and 81 days. The average duration of illness before admission to the hospital was 8 days; that of the four recovered cases, approximately 14 days.

Nine cases were associated with infections of the skin, of which six occurred in the face or neck; all succumbed. One fatal case began as an infection of the prostate, and one of a pilonidal cyst. One patient had acute bacterial endocarditis, but the portal of entry in this case was not determined. Two septicemias secondary to uterine infection were fatal. Four of seven patients with osteomyelitis died. Five other foci were either uncertain or entirely obscure; one of these patients recovered. The mortality in the seven cases of osteomyelitis was 57.1 per cent; in the 20 other cases the mortality was 95 per cent.

Careful study of the isolated organisms was not made. Four strains were designated as *Staphylococcus albus.* Six were identified as hemolytic *Staphylococcus aureus,* and 12 merely as *Staphylococcus aureus.* Colony counts were reported in eight instances. In two cases there were fewer than 25 colonies; in two cases there were from 25 to 100 colonies; and in four there were 100 or more colonies per cubic centimeter.

* The drugs used in this study were generously supplied by the Winthrop Chemical Company, E. R. Squibb & Sons, and The Lederle Laboratories, Inc.

During the period reviewed, treatment of several kinds was uniformly ineffective. Most of the patients received one or more blood transfusions and some received as many as twenty. Among the fatal cases, six patients received adequate doses of sulfanilamide and three of sulfapyridine; two patients were given bacteriophage, and five received a polyvalent antistaphylococcus serum prepared by Dr. Lee Foshay. Many patients received combinations of these forms of therapy.

TABLE I

Author	No. of Cases	Mortality	Remarks
Baker and Shands, 1939	30	70%	Staphylococcemia with osteomyelitis. "Routine" treatment.
Baker and Shands, 1939	35	25.7%	Staphylococcemia with osteomyelitis, treated with staphylococcus antitoxin.
Baker and Shands, 1939	36	60%	Cases other than osteomyelitis. Treatment expectant or surgical.
Baker and Shands, 1939	12	75%	Treatment expectant or surgical, plus staphylococcus antitoxin.
Dolman, 1934	32	78.1%	Staphylococcemia not associated with osteomyelitis. Staphylococcus antitoxin.
Dolman, 1934	32	32.3%	Staphylococcemia with osteomyelitis. Staphylococcus antitoxin.
Stookey and Scarpellino, 1939	117	91.4%	No cases of osteomyelitis. Assorted treatment.
Stookey and Scarpellino, 1939	17	53%	No cases of osteomyelitis. Staphylococcus antitoxin.
Julianelle, 1939	17	57%	Staphylococcus antiserum.
MacNeal and Frisbee, 1936	100	75%	Treated with bacteriophage.
Dutton, 1933	12	8.3%	Treated with bacteriophage.
P. S. MacNeal, 1939	9	33.3%	Treated with bacteriophage.
Gilbert, 1938	5	20%	Treated with bacteriophage.
Mendell, 1939	35	82.9%	Assorted treatment.
Lowenstein, 1931	18	77.7%	Supportive treatment.

Autopsies were performed in 16 of the fatal cases, including the two treated with thiazole compounds. The distribution of metastases is shown in table 2, and conforms, in general, with that ordinarily observed.

The four recovered patients include three cases of osteomyelitis, and one patient whose portal of entry was not definitely determined. All were acutely ill. The patients with osteomyelitis were treated by incision and drainage of the local lesion, followed by immobilization. In addition, they were given blood transfusions, and one patient received antistaphylococcal serum. The fourth recovered patient was a 41-year-old white man who was critically ill with metastases to the skin and conjunctiva; he also gave evidence of osteomyelitis of the left toe, though this infection was not manifest until the patient had been in the hospital several days. His treatment consisted of large doses of sulfapyridine, of transfusions of normal blood, and two transfusions of the blood of a donor previously immunized against several strains of staphylococci by Dr. J. A. Kolmer of Philadelphia.*

* Supplied through the kindness of the Philadelphia Blood Bank.

TABLE II

Distribution of Gross and Microscopic Abscesses Found at Autopsy in 18 Cases of Staphylococcal Septicemia

Organ	Number of Cases
Kidney	15
Myocardium	8
Lung	9
Spleen	8
Brain	5
Liver	5
Heart valves (mitral 5; aortic 2; tricuspid 1)	5
Intestine (ulcerative enteritis)	3
Pericardium	2
Mediastinal tissue, Endometrium, Myometrium, Parametrium, Prostate, Psoas muscle, Perinephric fat	1

His improvement was gradual but definite, though it was difficult to ascribe it to any one therapeutic measure. Three positive blood cultures were obtained when the sulfapyridine blood level varied between 6 and 13 mg. per cent, and one positive culture was obtained four days after the immunotransfusion. He was well five months after discharge.

REPORT OF PATIENTS TREATED WITH THIAZOLE DERIVATIVES

Case 1. This 14-year-old schoolboy was admitted to the Cincinnati General Hospital January 27, 1940, complaining of fever and malaise of four days' duration. A week before admission he had twisted his leg in the rung of a rocking chair, and six

TREATMENT AND LABORATORY TESTS

Case 1

Date	Blood Cultures	SMT Grams	SMT Blood Levels *	Blood Transfusions	Remarks
1–27–40	Non-hem. *Staph. aureus* 23 col./c.c.	5		500 c.c.	Incision and drainage—left tibia; cast applied. Pus from rt. zygoma = *S. aureus*. Pus from left tibia = *S. aureus*.
1–28–40	Non-hem. *Staph. aureus* 26 col./c.c.	5	Total: 2.5 mg. % Free: 0.9 mg. %	250 c.c.	
1–29–40	Neg.	7	Total: 2.0 mg. % Free: 0.6 mg. %	300 c.c.	
1–30–40	Neg.	11	Free: 0.8 mg. %		
1–31–40	Neg.	11	Free: 0.8 mg. %		
2– 1–40		12			
2– 2–40	Neg.	12	Free: 1.5 mg. %		
2– 3–40		9		250 c.c.	
2– 6–40				250 c.c.	

SMT = Sulfamethylthiazole.
Total Grams SMT = 72.
* Blood levels were determined by the method of Bratton and Marshall. Early determinations were read against a sulfapyridine standard and corrected for molecular weight; later sulfamethylthiazole was used as a standard.

days later the leg became swollen and tender. That day he had several chills. He noticed at the same time that the right side of his face was swollen and tender.

Physical examination revealed an acutely ill boy with a temperature of 101.8° F., pulse 120, respirations 20, and blood pressure 120 systolic and 88 diastolic. There was a red, tender, swollen area over the right zygoma. The left leg was swollen and tender from the ankle to the knee. The remainder of the physical examination was not remarkable.

The white blood cells numbered 22,000, the red blood cells numbered 4.34 million, and the hemoglobin 12.5 grams per cent. Blood culture yielded 23 colonies per cubic centimeter of a non-hemolytic *Staphylococcus aureus*.

Treatment consisted of oral sulfamethylthiazole, blood transfusions, and surgical intervention. An incision and drainage were performed at two points on the tibia, pus aspirated, and a cast applied. Another incision was made beneath the periosteum of the right zygoma, and pus removed. The relation between blood cultures and treatment is shown in the accompanying table.

The patient returned home with the left leg in a cast two weeks after admission. He later returned to the hospital, and six weeks after his first discharge from the hospital underwent a sequestrectomy. The lesion in the zygoma area healed during the first admission.

TREATMENT AND LABORATORY TESTS

Case 2

Date	Blood Cultures	SMT Grams	SMT Blood Levels	Blood Transfusions	Remarks
2–19–40	*Staph. aureus*				
	Staph. aureus				Incision and drainage—left humerus. Sub-periosteal pus yielded *Staph. aureus*.
2–20–40	1:00 p.m. 4 col.	4			
	8:30 p.m. neg.				
	10:45 p.m. neg.				
2–21–40	Neg.	24	6.3 mg. %	300 c.c.	
2–22–40		24	7.9 mg. %	500 c.c.	
2–23–40	Neg.	24		250 c.c.	
2–24–40		24	8.2 mg. %		
2–25–40		18			
2–26–40		6			
2–27–40		6	2.6 mg. %		
2–28–40		5			
2–29–40		4			
3– 1–40		6	3.9 mg. %		Cast applied.
3– 2–40		6			
3– 3–40		6			
3– 4–40		6			
3– 5–40		6			
3– 6–40		4			

SMT = Sulfamethylthiazole.
Total Grams SMT = 173.

Case 2. This 19-year-old messenger boy was admitted to the Cincinnati General Hospital on February 18, 1940, complaining of pain in the left arm and shoulder of eight days' duration. Eleven days before admission he had been aware of some "stiffness" of the left elbow, but had no pain at that time. Three days later, pain and swelling appeared in the left elbow and shoulder, pain that was aggravated by movement or palpation. The following day he had a chill. During the succeeding week, his temperature ranged from 102° to 104°. The boy was acutely ill, and suffered from nausea and vomiting.

On admission to the hospital, the temperature was 104.4°, the pulse 120, the respirations 24, and the blood pressure 136 systolic and 78 diastolic. He was acutely ill. Important physical findings were limited to the left upper extremity. There was some swelling of the entire left arm, from the wrist to the shoulder, but the maximum swelling and tenderness involved the upper arm. There were a few small discrete tender axillary nodes on the left.

The red blood cell count was 5.06 million, the hemoglobin was 13.4 grams per cent, and white blood cells numbered 14,400, with 85 per cent neutrophiles. The admission blood culture showed 92 colonies of *Staphylococcus aureus* per cubic centimeter. A roentgen-ray on February 20 showed evidence of osteomyelitis of the left humerus with slight periosteal elevation.

TREATMENT AND LABORATORY TESTS

Case 3

Date	Blood Cultures	SMT Grams	Blood Levels Free—mg. %	Blood Transfusions
2–15–40	*S. aureus* (Hemolytic)	3		
2–16–40		24		200 c.c.
2–17–40	*S. aureus* 1 col./c.c.	24	7.3	500 c.c.
2–18–40	*S. aureus* 2 col./c.c.	24	10.8	200 c.c.
2–19–40	*S. aureus* 2 col./c.c.	24	6.3	200 c.c.
2–20–40	*S. aureus* 1 col./c.c.	24	8.5	200 c.c.
2–21–40	*S. aureus* Plate neg.	24	9.5	200 c.c.
2–22–40	Neg.	24	7.0	200 c.c.
2–23–40	Neg.	24	8.7	200 c.c.
2–24–40	Neg.	6	9.0	200 c.c.
2–25–40		6	5.7	
2–26–40	Neg.	6	6.8	200 c.c.
2–27–40	Neg.	3	6.0	200 c.c.
2–28–40	Neg.	3	3.4	
2–29–40		3		
3– 1–40		3		
3– 2–40	Neg.	3	2.6	
3– 3–40		3		
3– 5–40	Neg.			

SMT = Sulfamethylthiazole.
Total Grams SMT = 231.

On the morning of February 20, the patient was started on sulfamethylthiazole. The same day incision and drainage were performed upon the left humerus and a large amount of subperiosteal pus containing staphylococci removed. The relation between cultures and therapy is shown in the accompanying table. Improvement was rapid at first, more gradual after the first few days. The temperature did not reach normal levels for three weeks. Sulfamethylthiazole was continued for six days following the operation. On March 1, a cast was applied to the arm, and a week later the patient was discharged. He was re-admitted to the hospital a month later to have the cast changed. At that time, roentgen-ray showed evidence of active subacute osteomyelitis, but no evidence of sequestration. By July 15, however, the local process had become so extensive that nearly all of the humerus had been destroyed.

Case 3. (Reported by courtesy of Drs. Richard Tyler and Ashton Welsh.) This patient was admitted to the Good Samaritan Hospital on February 5, 1940, complain-

ing of a carbuncle of the nose. Two weeks before admission, he had pulled a hair from the edge of the nares. Several days later the nose became red, tender, and swollen. Hot packs applied to the nose brought about no improvement, so the patient was brought to the hospital. He was a mild diabetic.

On admission to the hospital, the patient was acutely ill. The nose was swollen, deep purple, tender, and painful. The medial portion of the eyelids was swollen. The remainder of the physical examination was negative.

The hemoglobin was 82 per cent and the white blood cells numbered 15,850. The urine contained sugar, but no acetone. The blood sugar was 416 mg. per cent, and the CO_2 combining power 55 volumes per cent. Culture of pus from the nose yielded a hemolytic *Staphylococcus aureus*.

TREATMENT AND LABORATORY TESTS

Case 4

Date	Blood Cultures	SFMD Grams	SFMD Blood Levels	Blood Transfusions
2–22–40	Neg.			500 c.c.
2–23–40	Neg.			1000 c.c.
2–24–40		5		280 c.c.
2–25–40		6		250 c.c.
2–26–40		6	6.0 mg. %	200 c.c.
2–27–40		6	10.4 mg. %	250 c.c.
2–28–40		2		250 c.c.
2–29–40	*Staph. aureus*			250 c.c.
		SFPD	SFPD	
3– 1–40		2	Faint trace	270 c.c.
3– 2–40	*Staph. aureus*	6		250 c.c.
3– 3–40		6	5.2 mg. %	250 c.c.
3– 4–40		5	13.8 mg. %	250 c.c.
3– 5–40		4		
3– 6–40		4	12.1 mg. %	
		SMT		
3– 7–40	*Staph. aureus* 17 col.	4	Free 4.8 mg. % Total 5.7 mg. %	
3– 8–40	*Staph. aureus* 49 col.	9	7.9 mg. %	250 c.c.
3– 9–40	*Staph. aureus* 108 col.	9	6.3 mg. %	500 c.c.
3–10–40		9		
3–11–40	*Staph. aureus* 73 col.	9		
3–12–40	*Staph. aureus* 824 col.	4.5		

SFMD = Sulfanilamide.
SFPD = Sulfapyridine.
SMT = Sulfamethylthiazole.
Total Grams SMT = 44.5.

Despite roentgen-ray treatment and local magnesium sulfate compresses, the infection spread and on February 15, a blood culture yielded a hemolytic *Staphylococcus aureus*. Sulfamethylthiazole was begun the following day; the relation between blood cultures and therapy is shown in the accompanying table. The patient improved gradually, and was finally allowed out of bed on April 2. At that time, a bilateral foot drop was observed, and a neurological examination revealed that the knee jerks were diminished in both legs, and the ankle jerks absent. Muscle weakness was restricted to the feet. Vibratory, position, and pain perception were normal.

Case 4. This 32-year-old white woman was admitted to the obstetrical service of the Cincinnati General Hospital on February 20, 1940, in the seventh month of pregnancy, with a placenta praevia. A Brown bag was inserted, but removed at the end of

12 hours. At this time the membranes were ruptured and another bag inserted. Several hours later, a Braxton-Hicks version was performed and a dead fetus delivered. The placenta did not separate and had to be removed manually. Intrauterine and intravaginal packs were inserted. During the version, the patient had a chill, followed by elevation of her temperature to 105.6°. The patient was given sulfanilamide, 6 grams a day, for four days. Sulfapyridine was substituted but she continued to grow worse. She received 1 gram every 4 hours for six days, but showed no improvement. At the end of this period the patient was transferred to the medical service and sulfamethylthiazole begun. She was very ill, showed signs of patchy pneumonia with dyspnea and cyanosis, went rapidly down hill, and died six days after the institution of sulfamethylthiazole. The day before death, a pericardial friction rub was heard. The relation between the patient's course and treatment is shown in the accompanying table.

Postmortem examination showed acute suppurative endometritis and myometritis with retained placental polyp; miliary abscesses in the wall of the uterus; acute pyometritis; acute vegetative endocarditis of the mitral and tricuspid valves; miliary abscesses in the myocardium, lungs, and kidneys; purulent pericardial effusion with fibrino-purulent pericarditis; septic infarction of the spleen.

Case 5. (Reported through the courtesy of Drs. Leon Schiff and Joseph P. Evans.) This 28-year-old housewife was admitted to the Holmes Hospital on March 31, 1940, complaining of pain in the neck of nine days' duration. She had been in good health until nine days before admission, when she developed pain in the posterior cervical region, and limitation of motion in all directions. This pain gradually increased in severity, and radiated down the neck along the trapezii and down the arms to some extent. She had no chills. The temperature ranged from 99° to 101°. For two days before admission she received sulfanilamide, 4 grams a day.

On admission to the hospital she was acutely ill, cyanotic, and moderately drowsy. Temperature was 100.4,° pulse 104, and respirations 20. The neck was stiff, with marked tenderness over the cervical spines, greatest over the seventh spine. There was some tenderness laterally with spasms of the neck muscles posteriorly, including the trapezii. The remainder of the physical examination was negative.

The red blood cells numbered 3.59 million, the hemoglobin 10 grams per 100 c.c., and the white blood cells 13,700. Differential blood count showed 81 per cent neutrophiles, 13 per cent lymphocytes, and 5 per cent monocytes. Urine had a specific gravity 1.018, albumin one plus, and 10–12 white blood cells per high power field.

A tentative diagnosis of cervical osteomyelitis was made, though the only roentgen-ray evidence was the presence of thickening of the prevertebral fascia. She was given sulfanilamide. When a blood culture taken the day after admission revealed *Staphylococcus aureus*, the sulfanilamide was stopped, and sulfamethylthiazole begun. On April 1, the patient developed meningitis, and *Staphylococcus aureus* was recovered from the cerebrospinal fluid.

She was critically ill for several days. Stupor developed and the Kernig sign was present. The cell count in the spinal fluid rose to 1100 cells, of which the majority were polymorphonuclears. Hemolytic *Staphylococcus aureus* was recovered from the spinal fluid on four different days, and on one occasion cocci were found on the direct smear of the fluid. The patient received sulfamethylthiazole during this period, and the relationship between dosage, cultures and blood levels is shown in the accompanying table. Improvement was gradual but definite, and by April 9 her improvement was very distinct. On April 11, a generalized maculopapular rash appeared, sulfamethylthiazole was discontinued, and within two days the rash had vanished. A lumbar puncture performed on April 11 revealed evidence of probable block in the spinal canal, and six days later the block was complete. On April 19 roentgen-ray showed evidence of osteomyelitis of the fourth and fifth cervical verte-

brae, and a cast was applied to the neck. The following day, however, she developed numbness and definite weakness of the right arm and leg with loss of appreciation of pin prick in the distribution C4, 5, on that side, and over all the dermatomes of the left arm. A laminectomy involving the arches of C4, 5, 6, and

TREATMENT AND LABORATORY TESTS

Case 5

Date	Blood Culture	SMT Grams	Blood Levels mg. %	Blood Transfusions	C.S.F. Culture	Remarks
3–31–40	*S. aureus*					
4– 1–40	Neg.	4			*S. aureus*	
4– 2–40	*S. aureus*	4		500 c.c.		C.S.F.: 450 cells.
4– 3–40		8	2.0	500 c.c.		
4– 4–40		12	Less than 1		*S. aureus*	
4– 5–40	Neg.	15	1.4	250 c.c.		
4– 6–40	Neg.	18	3.6	250 c.c.	*S. aureus*	C.S.F.: 1100 cells.
4– 7–40		18	3.2			
4– 8–40	Neg.	18	3.2	250 c.c.	*S. aureus*	C.S.F.: 130 cells.
4– 9–40		18	3.6	250 c.c.		
4–10–40		14				
4–11–40		12				1.0 mg. % (SMT. Level in C.S.F.) Rash.
4–12–40	Neg.					
4–16–40	Neg.					
4–17–40						C.S.F. complete block. Laminectomy with bony decompression.
4–20–40		8				
4–21–40		18				
4–22–40		15	3.0			
4–23–40		8				Trace SMT Level in C.S.F.
4–24–40		4	1.8			
4–25–40				250 c.c.		Signs of probable peripheral neuritis.

SMT = Sulfamethylthiazole.
C.S.F. = Cerebrospinal Fluid.
Total Grams SMT = 194.

part of C3 was performed by Dr. J. P. Evans. Postoperative improvement was slow. On April 25, stocking anesthesia of both legs extending 5 cm. above the knees was noted and attributed to sulfamethylthiazole which had been resumed at the time of the laminectomy. The drug was again discontinued. The neurological signs on discharge were limited entirely to pyramidal tract disturbances and a suggestive level of hypesthesia, both subjective and objective, below the level of T8, bilaterally. She still had some numbness in the right arm and hand in addition to that which was present below T8. Strength for walking was adequate and proprioceptive sense was present.

Case 6. This 45-year-old painter was in good health until he fell off a scaffold on April 27, 1940, fracturing his nose and left arm. He was brought to the Cincinnati General Hospital where the fractured nose was set. Examination of the left arm revealed a small laceration on the lateral aspect of the elbow, with shortening of the arm and posterior displacement of the elbow. There was moderate swelling of the soft tissues. The arm was set and the patient put to bed.

On admission the temperature was 99.4°, pulse 76, respirations 18, and blood pressure 130 systolic and 70 diastolic. Though the patient was not at all ill in appearance, he ran a fever of 100–102° for a week. The temperature then fell to normal

for another week. At the end of that time, it was deemed advisable to perform an open reduction of the elbow. The day following the operation the temperature again rose to 102°, and fluctuated between normal and febrile levels for 11 days. Ten days after the operation, a wound infection was discovered, and a culture of the pus yielded

TREATMENT AND LABORATORY TESTS

Case 6

Date	Blood Cultures	ST Grams	ST Blood Levels Free—mg. %
5–19–40	*Staph. aureus* 1 col./c.c.	6	
5–20–40	*Staph. aureus* 2 col./c.c.	12	3.3
5–21–40		12	5.9
5–22–40		12	6.8
5–23–40		6	6.0
5–24–40		5	
5–25–40		0	

ST = Sulfathiazole.
Total Grams ST = 53.

Staphylococcus aureus. The following day, the patient suffered definitely chilly sensations, but no frank chill. Blood culture taken the next day yielded *Staphylococcus aureus* in broth, and one colony per cubic centimeter of blood on a plate. He was started on sulfathiazole. The relation between blood cultures and treatment is shown in the accompanying table. The patient made an uneventful recovery, the fever gradually subsided, and a week after discharge from the hospital felt well. At that time, the discharge from the wound had cleared considerably.

Case 7. (Reported through the courtesy of Dr. S. Taplitz.) This 67-year-old farmer was admitted to the Bethesda Hospital on June 3, 1940, in a semi-comatose condition. He had been in excellent health until a month before admission, when he

TREATMENT AND LABORATORY TESTS

Case 7

Date	Blood Cultures	Drug	Blood Level	Remarks
6–3–40	Hem. *St. aureus* 259 col./c.c.	Sod. SFPD, 4 gm. I.V.	23 mg. %	Staph. antitoxin 60,000 units.
6–4–40	Hem. *St. aureus* 536 col./c.c.	Sod. SFPD, 5 gm. I.V. Sod. ST. 5 gm. I.V.	22 mg. %	C.S.F.—sterile; 33 cells.
6–5–40	Hem. *St. aureus* 3870 col./c.c.	Sod. ST 5 gm. I.V.	18.2 mg. %	

SFPD = Sulfapyridine.
ST = Sulfathiazole.
C.S.F. = Cerebrospinal Fluid.
I.V. = Intravenously.

began to complain of malaise. Nevertheless he continued to work until five days before admission. That day he noticed a small discolored swelling on the right little finger, which he thought was due to a splinter. His wife opened the swelling with a

flamed needle. However, the patient's physician noticed similar areas on the toes the same day. The day before admission he became semi-comatose, developed rapid, deep respirations, and was admitted to the hospital.

On physical examination, the temperature was found to be 103° F., the pulse rate 110, and the respirations 25. There were questionable petechiae on the legs, under the finger nails, and on the soles of the feet. The neck was stiff. No cardiac murmurs were heard, but auricular fibrillation was present. The abdominal wall did not relax well, but no organs were felt.

The patient lived only two days after admission to the hospital. The day of admission he was given 4 grams of sodium sulfapyridine intravenously and 60,000 units of commercial staphylococcus antitoxin. The following day he was worse. The white blood cells numbered 21,000, with 89 per cent polymorphonuclears. The spinal fluid was clear and sterile on culture, but contained 33 cells per cubic millimeter. He was given another intravenous injection of 4 grams of sodium sulfapyridine, following which the treatment was changed to intravenous sodium sulfathiazole. The relationship between treatment and blood cultures is shown in the accompanying table.

Autopsy revealed acute vegetative endocarditis of the aortic valve, with perforation of the right posterior cusp. Abscesses were found in the myocardium, spleen, and kidneys. The cranial cavity was not opened.

Case 8. This 45-year-old taboparetic colored woman was admitted to the medical service of the Cincinnati General Hospital on July 1, 1940, because of dysuria, frequency, suprapubic and back pain, and chills of several days' duration. Several months previously, an arthrodesis had been performed on the patient's right knee, to correct a Charcot joint, and at the time of admission to the medical service, the right leg was still in a cast.

The temperature was 103°, pulse 110, respirations 30, and blood pressure 120 systolic and 70 diastolic. The patient exhibited moderate discomfort, but did not appear seriously ill. The heart and lungs were normal. There was definite bilateral costovertebral tenderness. The white blood count was 13,850, the red blood count 4,700,000, and the hemoglobin 15 grams. The urine was cloudy, contained 12 pus cells per high power field, and a small amount of albumin; culture yielded *E. coli*. The blood urea nitrogen was 21 mg. per cent.

On July 12, cystoscopy was performed. Though evidence of chronic cystitis was found, retrograde pyelograms were normal. The following day, the patient had a chill, and a blood culture yielded *Staphylococcus aureus*. The patient was started on sulfathiazole: the relationship between therapy and blood cultures is shown in the accompanying table. Several days later, she complained, for the first time, of pain in the right knee; the cast was removed, and though there was no evidence of osteomyelitis, 270 c.c. of purulent material containing *Staphylococcus aureus* were removed from the joint. The patient was transferred to the orthopedic service, where a through-and-through drainage of the joint was established. The joint continued to drain though the amount of drainage decreased over a period of several weeks.

During an investigation of a complaint of abdominal pain on August 12, a roentgen-ray revealed an infectious process involving L2 and L3, with destruction of large portions of these vertebrae. Nevertheless, the patient was afebrile and improved symptomatically. She left the hospital against advice on August 29.

Case 9. This 55-year-old white man had been perfectly well until about 11 days before admission to the hospital when he developed an influenza-like illness characterized by fever, malaise, generalized aching, and chilly feelings. Several days later a swollen tender area on the left fifth toe was incised by a physician, and a small amount of pus released. Whether this lesion began before or after the onset of generalized symptoms could not be determined. During the days preceding admission the patient noticed small papular lesions on the trunk, face, and extremities.

TREATMENT AND LABORATORY TESTS

Case 8

Date	Blood Cultures	Grams—Drug	Blood Level (Free)	Remarks
7– 2–40		SFMD—.67 gm.		
7– 3–40		SFMD—.33 gm.		
7– 4–40		SFMD—4 gm.		
7– 5–40		SFMD—3 gm.	4.7 mg. %	550 c.c. blood. SFMD discontinued.
7–12–40	*Staph. aureus*			
7–13–40				350 c.c. blood.
7–14–40	*Staph. aureus* 18 col. Non-hemolytic	ST—5		300 c.c. blood.
7–15–40	*Staph. aureus* 4 col.	ST—6	3.0	Knee joint fluid (*Staph. aureus*).
7–16–40		ST—5	2.4	
7–17–40	*Staph. aureus* 1 col.	ST—6	3.8	
7–18–40		ST—6		Knee drainage smear; clusters of gram positive cocci.
7–19–40	*Staph. aureus* 4 col.	ST—5		
7–20–40		ST—2	2.1	Drainage, right knee.
7–21–40		ST—1		
7–22–40	Neg.	ST—5	2.8	
7–23–40	Neg.	ST—6		
7–24–40		ST—6	3.3	
7–25–40	Neg.	ST—5		500 c.c. blood.
7–26–40		ST—5	4.3	
7–27–40		ST—5		
7–28–40	Neg.	ST—6		
7–29–40		ST—6	3.6	
7–30–40		ST—6		
7–31–40		ST—5	3.6	
8– 1–40	Neg.	ST—6		
8– 2–40		ST—5	3.3	
8– 3–40		ST—6		
8– 4–40		ST—3		
8– 5–40				No chemotherapy after 8–5–40.
8– 8–40	Neg.			

SFMD = Sulfanilamide.
ST = Sulfathiazole.
Total Grams ST = 111.

On admission, the patient appeared moderately but not critically ill. The temperature was 103.6°, pulse 112, respirations 36, and the blood pressure 106 systolic and 56 diastolic. Numerous small lesions, macular, papular, and pustular, were present on the trunk and extremities, including the palms and soles. There was an indurated, slightly tender, discolored lesion in the subcutaneous tissue of the left fifth toe; no pus exuded from the area. The breath sounds were suppressed at both lung bases, but no râles were heard. The heart sounds had a scratchy quality, and a soft systolic murmur was heard at the apex; no diastolic murmur was heard. The remainder of the examination was essentially negative.

The patient was given sulfathiazole by mouth, even before blood cultures were reported positive for *Staphylococcus aureus*. When there was no response to the drug, sulfamethylthiazole was substituted, but this agent was equally ineffective. The patient

TREATMENT AND LABORATORY TESTS

Case 9

Date	Blood Cultures	Grams—Drug	Blood Level (Free)	Remarks
8–29–40	Hem. *Staph. aureus* 282 col.	ST—2		
8–30–40	Hem. *Staph. aureus* 345 col. (9:30 a.m.) 217 col. (4:45 p.m.)	ST—10	3.4 mg. %	Blood transfusion 500 c.c.
8–31–40	Hem. *Staph. aureus* 555 col.	ST—2 SMT—5	5.0 mg. %	
9– 1–40	Hem. *Staph. aureus* 405 col.	SMT—9	5.0 mg. %	

ST = Sulfathiazole.
SMT = Sulfamethylthiazole.
Total Grams ST = 14.
Total Grams SMT = 14.

went rapidly down hill and died on the fourth hospital day. The relationship between therapy and blood cultures is shown in the accompanying table.

Autopsy revealed acute vegetative endocarditis of the mitral valve, with metastatic abscesses in the lungs, liver, spleen, kidneys, perinephric fat, small intestine, brain, and skin. In addition, there was inflammation of the subcutaneous tissue of the small toe of the left foot.

Case 10. This 60-year-old miner was admitted to the Cincinnati General Hospital with a 10-day history of chills, fever, sweats, cough, and pain in the right shoulder. He remained in bed during that period, and gradually became worse. For three months before, he had had a non-productive cough.

TREATMENT AND LABORATORY TESTS

Case 10

Date	Blood Cultures	Grams—Drug	Blood Level (Free)	Remarks
10–15–40		0		
10–16–40		SFPD—2		Blood urea nitrogen 65 mg. %.
10–17–40	*Staph. albus* innumerable	SFPD—4		Urine cult. = *S. albus.*
10–18–40	*Staph. albus* innumerable	ST—3		Blood urea nitrogen 87 mg. %. Bursal fluid = *S. albus.*
10–19–40	*Staph. albus* 178 col./c.c.	ST—6	4.9 mg. %	
10–20–40	*Staph. albus*	ST—6	6.8 mg. %	Blood urea nitrogen 98 mg. %.
10–21–40	*Staph. albus* 92 col./c.c.	ST—6	12.5 mg. %	Blood urea nitrogen 65 mg. %. Blood transfusion 500 c.c
10–22–40	*Staph. albus* 54 col./c.c.	ST—6	13.7 mg. %	Blood urea nitrogen 115 mg. %.
10–23–40		ST—1		

SFPD = Sulfapyridine.
ST = Sulfathiazole.
Total Grams SFPD = 6.
Total Grams ST = 28.

On physical examination he was found to be acutely ill, confused, and poorly nourished. The temperature was 102°, the pulse 100, the respirations 36, and the blood pressure 110 systolic and 60 diastolic. The heart was considerably enlarged, and a loud systolic murmur was heard all over the precordium, especially loud at the apex. There were râles at both lung bases and in the left axilla. The liver descended four fingers'-breadth below the costal margin. There was a large hard mass in the left flank believed to be the kidney. The right shoulder was painful on motion.

The red blood count was 4.34 million, the hemoglobin 12.4 grams, and the white blood count was 15,800 with 72 per cent polymorphonuclear neutrophiles. The urine was cloudy, contained two plus albumin, 5 to 15 white blood cells per high power field, innumerable red blood cells and occasional casts. The Kahn reaction on the blood serum was negative. The blood urea nitrogen was 65 mg. per cent, the CO_2 combining power 33 volumes per cent. Blood culture revealed thousands of colonies of *Staphylococcus albus* per cubic centimeter.

Before the results of the blood culture were known, the patient was given sulfapyridine, but sulfathiazole was substituted as soon as the staphylococci were recovered. The relation between blood cultures and treatment is shown in the accompanying table.

The course of the patient was rapidly down hill. Petechiae appeared on the trunk and legs, as well as on the conjunctivae. The systolic murmur noted on admission became louder. He died on the eighth hospital day.

Autopsy revealed acute vegetative endocarditis of the mitral valve, multiple miliary abscesses of the kidneys, unresolved pneumonia of the right lower lobe, cirrhosis of the liver, and acute toxic splenitis.

Case 11. This 71-year-old white man was ostensibly in good health until eight days before admission when he complained to his wife of pain in the right knee on standing or walking. A few days later he began to suffer from pain in the right hip. The next day he had several chills, followed by fever. For several months he had had symptoms of mild diabetes.

Physical examination revealed an acutely ill, but fairly well nourished old man who was somewhat irrational. The temperature was 104°, the pulse 116, respirations 26, and blood pressure 170 systolic and 90 diastolic. There were no skin lesions. Most of the teeth had been removed. The lungs were clear. The heart was moderately enlarged to the left, and a soft systolic murmur was heard at the apex. The right leg was held flexed at the hip and knee. The knee could be passively extended but only with considerable pain. Movement of the right hip joint in any direction caused pain. There was no redness, swelling, or local heat about either joint, though palpation over the posterior aspect of the hip joint caused sharp pain.

The red blood count was 4.9 million, and the hemoglobin 15 grams. The white blood count was 33,000, with 87 per cent neutrophiles. The urine contained four plus sugar and a trace of acetone, but was otherwise negative. The blood sugar was 308 mg. per cent, and the carbon dioxide combining power 40 volumes per cent. Blood culture yielded a non-hemolytic *Staphylococcus aureus*, 25 colonies per cubic centimeter. Roentgen-rays of the right knee and hip did not show evidence of osteomyelitis or pyarthrosis.

Sulfathiazole was begun on the third hospital day and continued for two weeks. The relationship between course and treatment is shown in the accompanying table. The patient's course was one of gradual improvement. On the second hospital day, one cubic centimeter of staphylococcus containing pus was aspirated from deep in the right gluteal region, but whether the pus came from the joint or from the soft tissues could not be ascertained. Further attempts at aspiration in the same region proved unsuccessful. After two weeks chemotherapy was discontinued, but the patient continued to have low grade fever, and though several consecutive blood cultures had been negative, a culture taken two weeks later yielded 15 colonies of staphylococci

TREATMENT AND LABORATORY TESTS

Case 11

Date	Blood Cultures	Grams—Drug (ST)	Blood Level (Free)	Remarks
9–14–40	*Staph. aureus* 25 col.			
9–15–40				Pus from gluteal abscess (*Staph. aureus*).
9–16–40	Non-hemolytic *Staph. aureus* 19 col.	7		
9–17–40	2 col.	6		
9–18–40	1 col.	6		
9–19–40	Neg.	6		
9–20–40	Neg.	6		
9–21–40	Neg.	6	3 mg. %	
9–22–40	Neg.	6		
9–23–40	Neg.	6	4.8 mg. %	
9–24–40	Neg.	6		
9–25–40		6	3.4 mg. %	
9–26–40	Neg.	6	3.9 mg. %	
9–27–40		6		
9–28–40		6	4.5 mg. %	
9–29–40		6		
9–30–40		1	1.8 mg. %	
10– 1–40	Neg.			
10– 2–40	Neg.			
10–15–40	*Staph. aureus* 6 col.	6		
10–16–40		6		
10–17–40		6	2.6 mg. %	
10–18–40		6		
10–19–40		6	6.6 mg. %	
10–20–40		6		
10–21–40	Neg.	6	3.4 mg. %	Urine—Non-hem. strep. *B. coli.*
10–22–40		6		
10–23–40		6		
10–24–40		6	2.6 mg. %	
10–25–40		6		
10–26–40		6	3.2 mg. %	
10–27–40		6		
10–28–40		2	5.0 mg. %	
10–31–40	Neg.			ST discontinued.

ST = Sulfathiazole.
Total Grams ST = 166.

per cubic centimeter. Sulfathiazole was given again with prompt sterilization of the blood stream. No new local foci appeared during this recrudescence. The drug was continued another two weeks when a bilateral conjunctivitis warranted its discontinuance. This complication disappeared as soon as the sulfathiazole was discontinued, but reappeared the following week when the patient was given the drug again. Improvement was steady, and the patient was discharged to a convalescent home, asymptomatic and afebrile.

Case 12. This 57-year-old housewife was admitted to the Surgical Service of the Cincinnati General Hospital for treatment of a large carbuncle of the neck, of three weeks' duration. She had suffered from diabetes mellitus for over a year, but since the onset of the carbuncle the diabetes had become more difficult to control.

TREATMENT AND LABORATORY TESTS

Case 12

Date	Blood Cultures	Grams—Drug (ST)	Blood Level	Remarks
10–13–40				X-ray therapy.
10–14–40				X-ray therapy—Incision and drainage.
10–15–40				X-ray therapy.
10–16–40				X-ray therapy.
10–17–40	*Staph. aureus* 11 col./c.c.	7		X-ray therapy.
10–18–40		6		
10–19–40	Neg.	8	3.9 mg. %	500 c.c. blood.
10–20–40	Neg.	6		
10–21–40	Neg.	5	1.9 mg. %	Incision and drainage.
10–22–40	Neg.	7	3.5 mg. %	250 c.c. blood.
10–23–40	Neg.	7		250 c.c. blood.
10–24–40	Neg.	13	3.3 mg. %	250 c.c. blood.
10–25–40		7	7.6 mg. %	250 c.c. blood.
10–26–40				250 c.c. blood.
10–27–40		Na SFPD		250 c.c. blood.
11– 2–40		5		150 c.c. blood. Excision of carbuncle.
11– 3–40	Neg.	5		
11– 4–40		(ST) 3	1.6 mg. %	500 c.c. blood.
11– 5–40		4		250 c.c. blood.
11– 6–40	Neg.	6	1.5 mg. %	250 c.c. blood.
11– 7–40		3		250 c.c. blood.
11– 8–40			Neg.	250 c.c. blood.
11– 9–40				250 c.c. blood.
11–10–40				Excision of carbuncle.
11–11–40				250 c.c. blood.
11–12–40			Trace	250 c.c. blood.
11–13–40		1		
11–14–40		1.5		
11–15–40		1		
11–16–40				

ST = Sulfathiazole.
Na SFPD = Sodium Sulfapyridine.
Total ST = 85.5.
Total Na SFPD = 10.

On physical examination she was found to be acutely ill, with a temperature of 101.6°, pulse of 90, respirations 20, and blood pressure of 110 systolic and 80 diastolic. There was a large carbuncle on the back of the neck, with a linear transverse area of necrosis draining pus. The cervical nodes were slightly enlarged and tender bilaterally. The remainder of the physical examination was essentially negative.

The white blood count was 20,000 and the hemoglobin 17 grams. The urine contained four plus sugar but no acetone. The blood sugar was 333 mg. per cent and the CO_2 combining power 50 volumes per cent.

Roentgen-ray therapy was begun and continued for five days. On the second hospital day, a radical incision and drainage were performed. On the fifth hospital day, because of a chill, a blood culture was taken and sulfathiazole started. The blood at that time was found to contain 11 colonies of *Staphylococcus aureus* per cubic centimeter, but was subsequently sterile. The relationship between cultures and treatment is shown in the accompanying table. Improvement followed, with remission of fever, but a local extension of the process a week later necessitated

another incision and drainage, followed by a radical excision of the carbuncle several days later. At the time of the present report, the carbuncle is healing and progress is considered satisfactory.

Discussion

In the thiazole derivative group, the only deaths that occurred were associated with acute bacterial endocarditis, a condition which still resists the best efforts of the therapist. If these cases are disregarded, the small series represents eight consecutive cases in which clearing of the blood stream took place after invasion by staphylococci. There is no doubt that any or all of these patients might have survived had they received only supportive treatment, for the literature is replete with single case reports of patients who have made remarkable recoveries from this highly fatal disease. Moreover, three of our cases were associated with osteomyelitis. Nevertheless, the recovery of eight consecutive acutely ill patients indicates that the thiazole compounds should be given further trial. Study of these cases adduces no evidence of any effect upon the local lesions.

Some of our experience has been with sulfamethylthiazole, whose toxicity seems to be greater than its non-methylated analogue.[13] In this series, two cases of peripheral neuritis were observed in patients treated with sulfamethylthiazole, but none in the sulfathiazole series. However, this complication occurred at the beginning of our experience with the drugs, when we were using larger doses than we later found necessary. Whether peripheral neuritis would have occurred had smaller doses been employed we cannot say. The "minor toxicities"—nausea, vomiting, rashes—appeared to be less frequent in patients receiving sulfamethylthiazole.

Summary

1. Twelve consecutive cases of staphylococcal septicemia were treated with thiazole derivatives of sulfanilamide. Eight recovered.

2. In all the fatal cases, endocarditis was present at autopsy.

3. A skin rash and an instance of peripheral neuritis were probably attributable to sulfamethylthiazole. Conjunctivitis and chills and fever were observed as examples of sulfathiazole toxicity.

4. Between the years 1933–1939, 27 cases of staphylococcal septicemia were recorded at the Cincinnati General Hospital, with only four recoveries.

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PREMONITORY SYMPTOMS OF ACUTE CORONARY OCCLUSION; A STUDY OF 260 CASES *

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THE symptoms of occlusion of the coronary artery are now well known, and the diagnosis of the acute attack is generally made with little difficulty. It is only recently, however, that attention has been paid to prodromes of the attack. Recognition of these premonitory symptoms is important both from a diagnostic and a therapeutic standpoint. Thus, the realization that a sudden onset of chest pain may presage the onset of coronary occlusion within a few hours or days will lead to earlier diagnosis of the impending attack and indicate immediate bed rest. Knowledge of such premonitory pain is essential in attempting to correlate the clinical history or mode of onset of the attack and the pathological findings in the heart, or to evaluate the various theories of the pathogenesis of coronary occlusion.

Premonitory pain or discomfort in the chest prior to an attack of acute occlusion of the coronary artery was mentioned early by several authors,[1-5] and several cases have been reported[6, 7] in which there was well marked prodromal pain. A study of the 145 case histories presented by Levine[8] in his classical monograph reveals that some form of premonitory pain was observed in only twelve. Similarly Bean[9] reported an incidence of only 9.3 per cent in 300 cases studied by him. On the other hand, Feil[10] estimated that approximately 50 per cent of the cases in his series showed a history of premonitory pain. The low incidence reported by Bean may be due to the fact that his series consisted of autopsy cases collected since 1922, and he had not been able to obtain detailed histories at first hand. This probably applies in part also to the cases of Levine. Feil,[10] Sampson and Eliaser,[11] and more recently, Langston,[12] have described in detail the clinical characteristics of the premonitory pain, respectively in 15, 29, and 5 cases of coronary occlusion, and have emphasized their importance.

MATERIAL AND FINDINGS

This study is based on detailed histories which were carefully elicited by the authors in 260 cases of acute coronary occlusion. A questionnaire was especially prepared[13] concerning the occurrence of angina pectoris previous to the attack, the occurrence of any symptoms as far back as four weeks prior to the attack, and the physical and emotional activities associated with them.

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Character of Premonitory Symptoms. Premonitory symptoms were found to have occurred in 115, or 44.2 per cent of the cases studied. Their character, time of occurrence, and precipitating factors are presented in tables 1 and 2. The most common symptom was substernal or precordial

TABLE I

Premonitory Symptoms in Coronary Occlusion; Their Character and Time of Appearance before the Attack

Symptoms	No. of Cases	Appearance before Attack										
		Less 1 hour	1–6 hours	7–12 hours	12–24 hours	1 day	2 days	3 days	4–6 days	1 week	2 weeks	3 weeks
Chest or precordial pain	26	0	2	2	9	1	5	4	2	1	0	0
Sudden appearance of anginal syndrome	15	0	0	0	0	0	1	1	1	6	4	2
Increasing anginal syndrome on exertion	8	0	0	0	0	0	0	1	1	2	3	1
Chest or precordial discomfort (coldness, heaviness, fullness in chest)	17	0	4	2	4	2	1	0	1	1	2	0
Pain in arms or shoulders	4	1	0	0	1	1	0	0	0	0	1	0
Dyspnea	4	0	0	0	3	0	0	0	1	0	0	0
Palpitation	3	0	0	0	1	0	1	0	0	1	0	0
Fatigue, weakness or "did not feel well"	22	0	4	0	9	1	3	0	1	2	2	0
Gastric symptoms	10	0	4	0	2	0	0	3	1	0	0	0
Nervousness, dizziness, coldness or feeling of heat	6	4	1	1	0	0	0	0	0	0	0	0
Total premonitory symptoms	115	5	15	5	29	5	11	9	8	13	12	3
No premonitory symptoms	145											
Total cases	260											

TABLE II

Precipitating Factors of the Premonitory Symptoms of Coronary Occlusion

Symptoms	No. of Cases	Precipitating Factors (70 cases)					Associated Factors (8 cases)		
		Rest	Mild Activity	Moderate Activity	Walking	Unusual Activity	Excitement	Meals	Cold
Precordial pain	20	7	6	1	3	1	0	2	0
Sudden angina pectoris	7	0	1	2	4	0	6	0	0
Increasing angina pectoris	9	0	0	3	6	0	0	0	0
Precordial discomfort	11	3	1	4	2	1	1	0	0
Pain in arms	4	1	1	0	0	0	0	1	1
Dyspnea	4	2	0	1	1	0	0	0	0
Palpitation	2	2	0	0	0	0	0	0	0
Weakness; "did not feel well"	9	2	2	2	0	0	2	2	0
Gastric symptoms	2	1	1	0	0	0	0	0	0
Nervousness, dizziness, etc.	6	2	1	1	1	0	0	1	0
Total	80	20 (28.5%)	15 (21.4%)	16 (22.8%)	17 (24.3%)	2 (2.9%)	3	6	1

pain, which occurred in 49, or 43 per cent, of the 115 patients (table 1). Seventeen other patients experienced vague discomfort in the chest, such as fullness, heaviness, coldness, or burning. Pain in the arms or shoulders occurred in four patients. In 15 of the 43 patients presenting chest pain, an anginal syndrome developed suddenly on effort or excitement, several days or weeks before the onset of the attack (see case report); in eight

patients an anginal syndrome had been present for some time but there was a sudden increase in the severity and frequency of the pain immediately preceding the attack of occlusion. Other cardiac symptoms noted prior to the attack were dyspnea (four cases) and palpitation (three cases).

A large group of cases presented prodromes other than cardiac pain. Twenty-two patients noted fatigue or weakness or "did not feel well," and 10 suffered gastric symptoms such as nausea, epigastric distress, a sensation of fullness, or abdominal pain. Occasional miscellaneous symptoms included nervousness, dizziness, and a feeling of coldness or of warmth (6 cases).

Time of Onset and Duration of Symptoms. In half the cases, the premonitory symptoms appeared within 24 hours of the acute attack (table 1). In a little over one-third they occurred from two to seven days, and in the remainder from two to three weeks before the occlusion. Among the 23 patients who developed angina on effort, the symptoms often appeared several days or weeks preceding the attack. In eight cases they preceded it by one week, in seven cases by two weeks, and in three cases by three weeks. In the series of Sampson and Eliaser premonitory pain appeared from three to five weeks prior to the occlusion in two of the 29 cases.

The duration of the premonitory symptoms varied. In many cases there was a single attack of pain lasting from a few minutes to several hours, after which the patients would be free of pain until the onset of occlusion. In others the seizures of pain or discomfort were transient and recurrent, and not infrequently the pain was continuous for several hours or days. The duration of the warning attack in the series of cases reported by Sampson and Eliaser also varied from a few minutes up to 14 hours. In Feil's series the premonitory pain lasted from 12 to 48 hours in eight of the 15 cases and from three to four weeks in two cases.

Precipitating Factors. The activity of the patients immediately preceding the premonitory attack could be elicited in 70 of our 115 cases. (Table 2.) The onset occurred during rest in 28.5 per cent of the cases, during mild activity in 21.4 per cent, during moderate activity in 22.8 per cent, and while walking in 24.3 per cent. In no one case did the symptoms begin during sleep, but several patients were aware of pain immediately upon rising. Unusual exertion occurred in only two cases (2.9 per cent). In 10 other cases the onset was associated with a secondary factor such as meals (six cases), excitement (three cases), and cold (one case). Mild activity included routine activities at home, standing in the street, sitting at a meeting, etc. Moderate activity included working, shopping, fishing, etc. The two instances of unusual activity were shoveling snow and an automobile accident. In the three cases associated with excitement, two patients were attending a wedding and one was suffering from anxiety.

Case Report. The following case of acute coronary occlusion was characterized by a prodromal period of five days' duration, during which the im-

pending occlusion was suspected from the sudden appearance of a typical anginal syndrome.

M. T., a male cutter, aged 45 years, was seen for the first time in March 1937. He complained of attacks of diarrhea, and an occasional stabbing pain in the region of the left nipple. The pain was not related to effort, meals, or excitement. It was mild and did not interfere with the patient's work. It usually persisted for several hours or days and was not relieved by nitroglycerin. The patient possessed an extremely emotional make-up. A complete physical examination revealed no abnor-

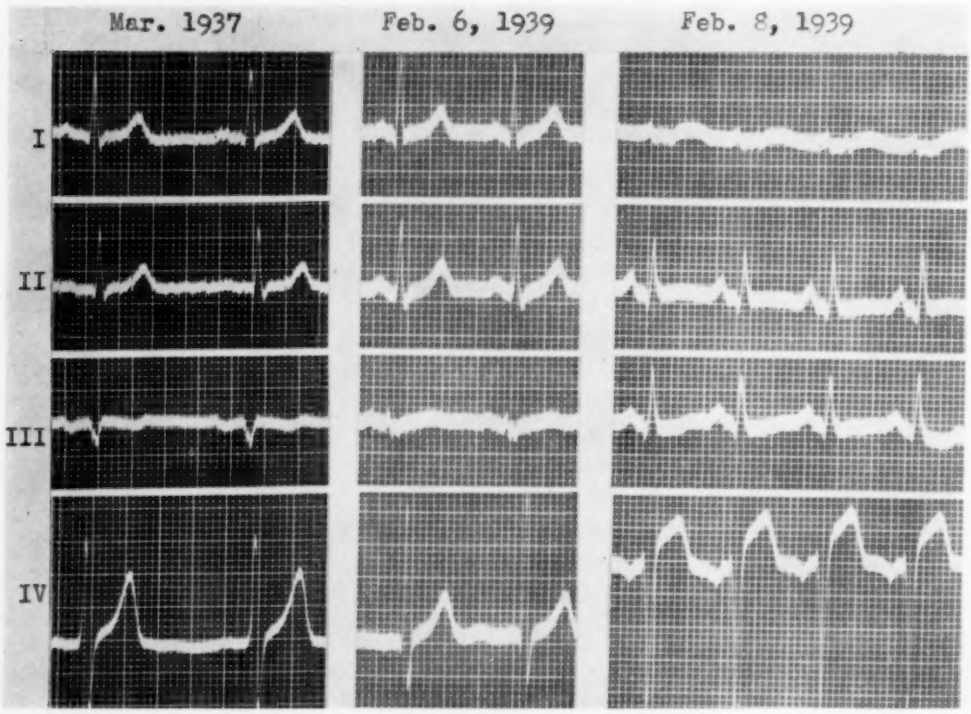

FIG. 1. M. T., Male, 45. Acute coronary occlusion, Feb. 7, 1939. Electrocardiograms during premonitory stage and after attack.

A. March 1937. Two years before attack. Electrocardiogram is entirely normal.
B. Feb. 6, 1939. Five days after onset of premonitory pain. Electrocardiogram is still normal. There is practically no change from previous record.
C. Feb. 8, 1939. One day after attack. Electrocardiogram is now typical of acute anterior wall infarction. The QRS complex is W-shaped in Lead I and the initial positive deflection in Lead IV (R–4) is very small. The S–T transition is elevated in Leads I and IV and the T-waves are very low in the standard leads.

mality except for the presence of mucous colitis. The heart was not enlarged. The sounds were of good quality and there were no murmurs. Blood pressure was 120 mm. Hg systolic and 80 mm. diastolic. Fluoroscopy confirmed the normal size and shape of the heart. The electrocardiogram (figure 1A) was entirely normal.

In view of the negative cardiac findings and the fact that the precordial pain had none of the characteristics of an anginal syndrome due to disease of the coronary artery, the pain was considered to be extracardiac, and possibly of psychogenic origin. The mucous colitis also was attributable to psychic causes.

The symptoms persisted for two years without significant change, but the attacks of pain became milder and less frequent. During a two-weeks' sojourn in the country in January 1939, the pain ceased entirely, despite considerable walking. About two weeks after the patient's return, however, he began to notice a new kind of pain that occurred only when he walked. It was localized beneath the sternum and was of an oppressive character, which caused him to stop after walking half a block. On standing still, the pain stopped.

The patient was seen five days after the onset of this typical anginal syndrome, but examination revealed no departure from the normal findings of the previous two years. The electrocardiogram was unchanged (figure 1B). Nevertheless, we suspected that an occlusion of the coronary artery was in process of formation, and the patient was placed in bed. After a comfortable night, he was awakened by an excruciating substernal pain that required several injections of morphine before he felt relief. The syndrome was now typical of acute coronary occlusion, with a heart rate of 140 and gallop rhythm. On the following day the blood pressure had fallen to 90/70, and a pericardial friction rub was audible. The electrocardiogram presented the typical Q_1, T_1 pattern of anterior infarction (figure 1C).

General Considerations

It has been shown that in over two-fifths of our cases the onset of acute coronary occlusion was preceded by premonitory symptoms lasting for several hours, days, or even weeks. This suggests that the arterial occlusion develops gradually in a large proportion of cases, a view which is consistent with recent pathological studies [14-16] concerning the mechanism of formation of coronary occlusion. These have demonstrated that the occlusion can form in three ways: Usually it is initiated by a hemorrhage into the intima of an arteriosclerotic plaque, with secondary thrombosis within the lumen as a result of injury or actual dissolution of the overlying endothelium. Less frequently there is a primary thrombosis on an arteriosclerotic plaque. In rare instances a hemorrhage into an atheromatous abscess (hematoma) closes the lumen without actual thrombosis.[17] Careful examination of the site of occlusion has produced evidence [16, 18] in some cases that the occlusion did not form suddenly but was produced by progressive or recurrent intramural hemorrhage or thrombosis. Thus, the hemorrhage within the plaque may show signs of organization while the thrombosis within the lumen may be of more recent appearance (figure 2); that is, the intramural hemorrhage may have occurred hours or days prior to the actual thrombosis. Again, the thrombus itself may not be uniform in appearance; its base adjacent to the plaque may show organization and fibroblastic formation, while the parietal portion may show a recent process.

On the basis of these observations it is possible to assume that the onset of the premonitory symptoms is associated with the rupture of a mural capillary, with hemorrhage, which suddenly narrows the lumen of the coronary artery but does not entirely block it. After a variable interval the lumen becomes completely obliterated as a result of the gradual formation of a secondary thrombus or of recurrent intimal hemorrhages, and it is only then that the acute symptoms appear. The process may take hours or days, and the

symptoms of complete occlusion may not occur for several weeks; during this period clinical evidence of coronary insufficiency is frequently observed, in the form of increasing angina pectoris.

A correlation of the factors often supposed to bring on the premonitory symptoms with the pathological observations presented above is also of interest. In previous reports [18, 19, 20] we have presented evidence to prove that effort and excitement were not factors in the precipitation of acute coronary occlusion. It was shown that the percentage of attacks which occurred during sleep, rest, mild or routine activity, walking, moderate activity, or strenuous exertion, coincided with the percentage of the day spent by the ordinary person in these activities. This indicated that the circumstances preceding the attack were coincidental and that none of them was causally related to the coronary occlusion. The latter is the end result of an arteriosclerotic process and is entirely fortuitous. In this paper it has been shown that premonitory symptoms occurred during rest in over one-fourth of the cases, and during the mild or moderate activity or walking that is routine in daily life in the remaining three-fourths. But the symptoms were associated with strenuous effort in only two cases. Therefore, we believe that, as in the case of the complete occlusion, effort did not initiate the process resulting in premonitory symptoms. Were effort a factor, the incidence of strenuous exertion would be much greater than 2.9 per cent. It is our opinion that the premonitory pain results from a purely arteriosclerotic process, whose origin and progress are unrelated to physical activity or rest.

The association of premonitory symptoms with some activity in slightly over two-thirds of the cases can readily be explained on a physiological basis. During the process of thrombus formation, the blood-flow through the narrowed lumen of the coronary artery may be sufficient for the resting needs of the myocardium, but it is inadequate when the oxygen requirement of the heart is increased by activity. Therefore, premonitory pain is apt to appear with exertion, as in angina pectoris. This may account for the fact that premonitory symptoms did not occur in sleep. When complete occlusion occurs, however, the coronary flow is inadequate even at rest, and the sudden severe ischemia results in the characteristic onset of acute, prostrating pain usually at rest.

Differentiation of the attack of premonitory pain from actual arterial occlusion was often difficult, particularly when the pain was severe or persisted for several hours. In such cases it was also difficult to determine the exact time of onset of the clinical attack of coronary occlusion. Certain clinical observations made by Feil and Sampson and Eliaser, as well as by ourselves, however, are helpful in the recognition of premonitory pain. These authors showed that during the premonitory attack and until the onset of the arterial occlusion there usually were no clinical indications of complete occlusion or myocardial infarction. As a rule the patient was not confined to bed, and fever, leukocytosis, tachycardia, a drop in blood pressure, and other objective

evidences of myocardial infarction were lacking. In fact, after the initial attack of premonitory pain the patient was often symptom-free until the occlusion occurred. Furthermore, electrocardiograms taken during this period were usually normal, or showed no definite evidence of recent infarction.

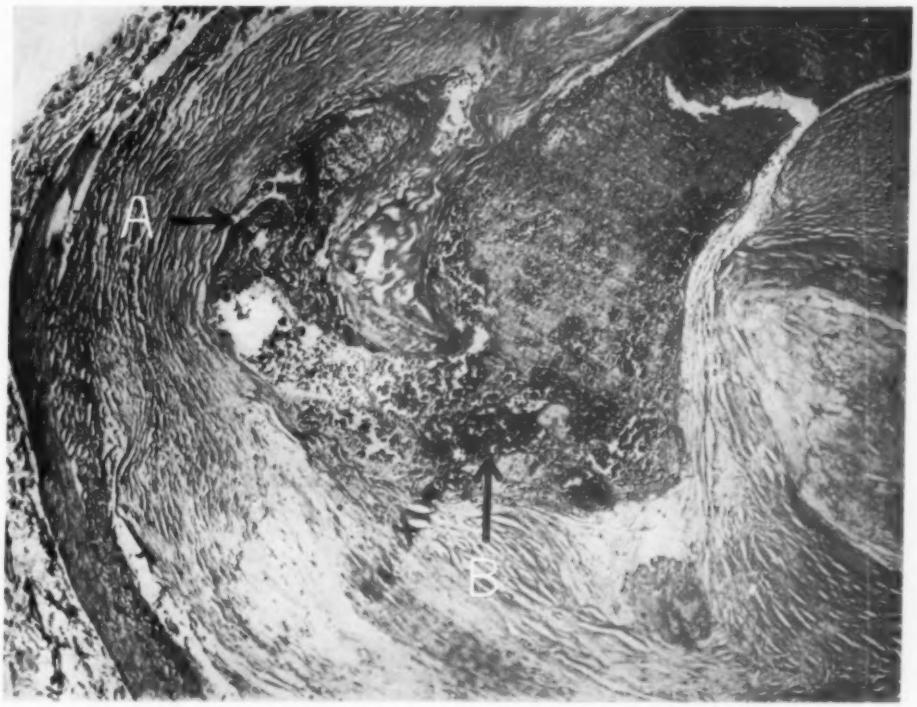

FIG. 2. Medium power magnification of section through a recent coronary artery thrombosis secondary to dissolution of the intima of recurrent intimal hemorrhage. Fibrinoid transformation of the zone of hemorrhage within the intima (A) indicates an origin antedating the thrombosis within the lumen (B).

The patients in our series presented a similar clinical course. Many of them suffered only a single attack of premonitory pain and were then symptom-free for several hours or days. Others suffered repeated attacks of angina pectoris but were symptom-free in the intervals between attacks and remained ambulatory. On the other hand, a large group of patients suffered from persistent precordial discomfort or from progressive weakness, but presented no other symptom of acute occlusion. Electrocardiograms of three patients were obtained during the period of premonitory pain (figures 1, 3, and 4). It is seen that evidence of acute infarction is lacking in the initial record of each case despite the occurrence of precordial pain of several hours' duration. It is only in the later records taken following the onset of the occlusion as determined clinically, that the classical signs of infarction appear.

The absence of clinical or electrocardiographic signs of acute infarction during the stage of premonitory symptoms indicates that a gradually pro-

gressing coronary occlusion does not result in myocardial infarction until the occlusion is complete. However, during the partial occlusion coronary insufficiency is present, as demonstrated by the appearance of premonitory pain. It is thus difficult to explain the almost complete absence of acute electro-

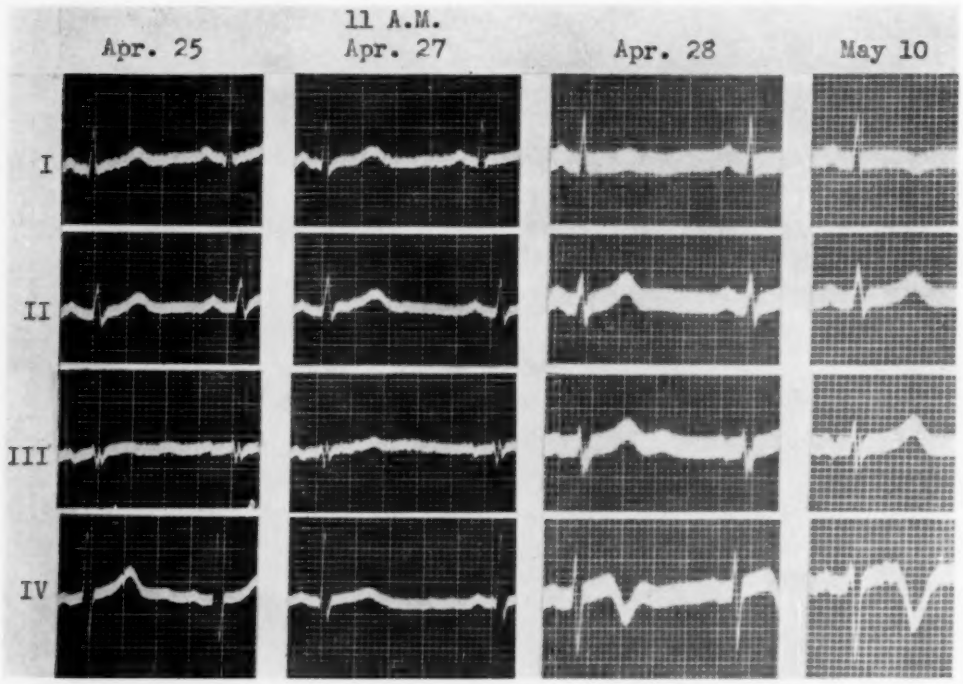

FIG. 3. N. G., Male, aged 55. Acute coronary occlusion April 27, 1939. Electrocardiograms during premonitory stage and following the attack.

A. April 25, 1939. Slight pressure in chest six days ago while in movie. Awakened from sleep one day ago by precordial pressure, which was persistent. Electrocardiogram is entirely normal.

B. April 27, 1939. 11 a.m. Persistent precordial pressure (premonitory pain). Electrocardiogram is still entirely normal. Severe attack of precordial and substernal pain occurred subsequently at 4 p.m.

C. April 28, 1939. One day after attack. Electrocardiogram is now characteristic of anterior wall infarction. T_1 is low and semi-inverted, T_4 diphasic, and T_3 higher and upright.

D. May 10, 1939. Two weeks after attack. Further progressive changes have occurred. T_1 is now inverted and coveplane. The initial positive deflection in Lead IV (R_4) is now very small.

cardiographic changes, since acute coronary insufficiency, by producing anoxemic changes in the myocardium, often results in depression of the S–T transition and lowering of the T-waves. Lowering of the T-waves occurred in three of the cases reported by Feil, but we encountered none in our cases. One of the cases, however, presented slight depression of the S–T transition in Leads I and II (figure 4). It is possible that greater changes would appear if the electrocardiogram were taken during effort.

The possible recognition of an impending coronary occlusion by the

appearance of premonitory symptoms raises the question of whether the occlusion can be prevented by prompt bed rest. We believe that once the occlusion has commenced to form, its progression to complete obstruction of the coronary vessel cannot be prevented. In fact, we have been able to

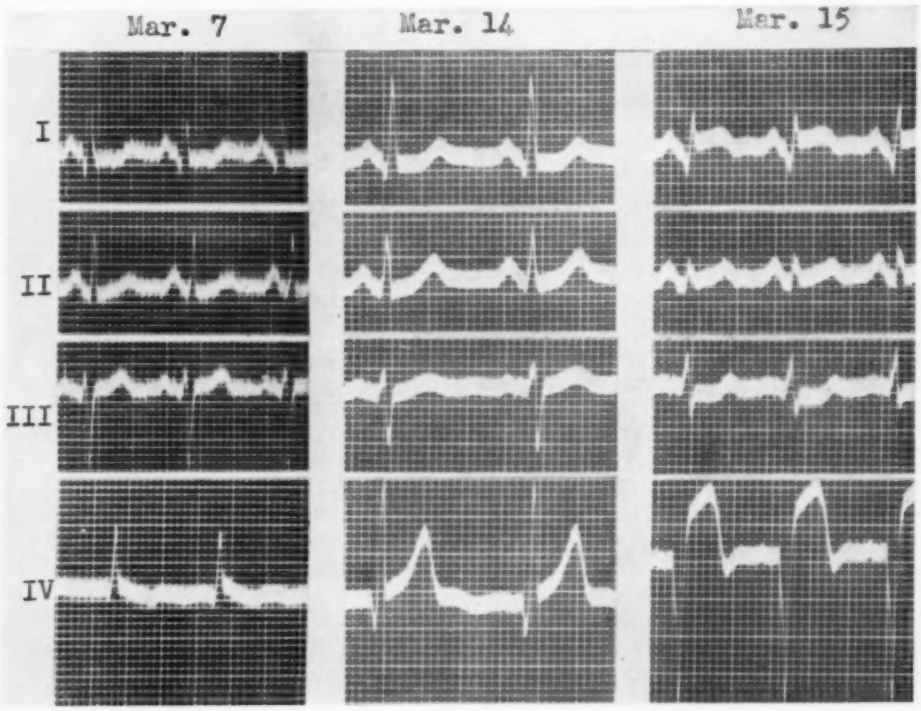

FIG. 4. L. E., Male, aged 50. Acute coronary occlusion, March 14, 1939. Electrocardiograms during premonitory stage and following attack.

A. March 7, 1939. Typical angina pectoris on effort for three months. The electrocardiogram shows left axis deviation, small Q_3, S–T depression in Lead I, and inverted T_3. The changes are abnormal and indicate coronary artery disease.

B. March 14, 1939. Persistent premonitory pain for one day. Record taken several hours before attack of occlusion. The Q_3 is larger, S–T transition is depressed in Leads I and II, T_3 is high and upright, and T_1 and T_2 higher. Although definite changes have occurred since the previous tracing, the record is not typical of acute infarction. The slight S–T depressions suggest coronary insufficiency.

C. March, 15, 1939. Twelve hours following attack of coronary occlusion. The record is now characteristic of acute anterior wall infarction. Q_1 and Q_3 are deep, and the S–T transition is elevated in Leads I and IV, depressed in Lead III.

collect a group of 60 patients in whom occlusion occurred after they had been bed-ridden and at complete rest for weeks or months. Thirty of these patients are included in the present series, and six of them exhibited premonitory symptoms. The cases illustrated in figures 1, 3, and 4 also followed a typical clinical course to complete coronary occlusion despite immediate bed rest during the prodromal stage. However, placing the patient in bed immediately following the onset of premonitory symptoms may de-

crease the severity of the symptoms and of heart failure following complete occlusion, and thereby decrease the mortality rate. This point, as Sampson and Eliaser have stated, can be determined only by the study of a large series of cases in which a diagnosis of impending coronary occlusion is made and corroborated by subsequent events.

Summary and Conclusions

1. Premonitory symptoms were present in 44.2 per cent of 260 patients with acute coronary occlusion from whom detailed histories could be elicited.

2. In most cases the premonitory symptoms consisted of substernal or precordial pain or discomfort. Other prodromes were fatigue, weakness, gastric distress, dyspnea, palpitation, nervousness, and dizziness.

3. The sudden appearance of a typical anginal syndrome or the sudden acceleration of a previously existing anginal syndrome frequently preceded the attack of occlusion.

4. The premonitory symptoms usually appeared within 24 hours prior to the acute attack, but in some cases they began two or three weeks before.

5. The duration of symptoms varied from a few minutes to several hours. Although the premonitory pain was usually intermittent or continuous, a pain-free period frequently intervened before the onset of acute occlusion.

6. The onset of premonitory symptoms occurred during rest in 28.5 per cent of the cases, during mild or moderate activity or walking in 68.5 per cent, and during strenuous effort in 2.9 per cent.

7. The premonitory symptoms were not associated with clinical evidence of myocardial infarction. Fever, leukocytosis, tachycardia, drop in blood pressure, and characteristic electrocardiographic changes were absent. These factors are significant in differential diagnosis.

8. The anatomic basis for the premonitory symptoms is assumed to be a gradual occlusion of the lumen of the coronary artery by progressive or recurrent intramural hemorrhage or by primary thrombosis on a plaque, which many take hours or days for completion. The initiation and progression of coronary occlusion occurs irrespective of physical activity or lack of activity. However, the physiological coronary insufficiency and myocardial ischemia which ensue may result in precordial pain, which is often brought on or intensified by effort.

9. Early recognition of the premonitory symptoms should lead to a reduction of heart failure and decrease the mortality rate by means of immediate bed rest, which, however, will probably not prevent the impending occlusion.

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CLINICAL EXPERIMENTS WITH MIXTURES OF STANDARD AND PROTAMINE ZINC INSULINS *

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EVANESCENT action is one of the major disadvantages of standard insulin. Protamine zinc insulin overcomes this difficulty. Its absorption from the site of injection is slow; its therapeutic action is prolonged. But precisely because of its retarded action, short periods of post-prandial hyperglycemia and glycosuria are common with its use. If separate additional injections of standard insulin are given for the purpose of eliminating this objectionable feature, then one of the major advantages of protamine zinc insulin, a reduction in the number of injections, is partly or wholly lost.

Mixtures of the two forms of insulin in the same syringe have been given in attempts to retain the advantages of each. Campbell, Fletcher and Kerr [1] were "successful by using a long, narrow-bore syringe, and some care in avoiding mixing of the fluids, in giving the two insulins in a single syringe." Graham [2] used a similar method and emphasized that "It is important to prevent the possibility of mixing the two insulins in the bottles as the prolonged contact might cause a definite change." He attempted to avoid undue mixture by taking the protamine insulin first into the syringe and then the lighter "ordinary insulin remains in the upper part of the syringe" near the needle. Another method was suggested by a correspondent in a letter to the editor of the Journal of the American Medical Association.[3] The writer stated that he gave a preliminary injection of standard insulin, removed the syringe from the needle, leaving the latter "sticking in the flesh," refilled the syringe with protamine zinc insulin, using another needle, and then, after removing the second needle from the syringe, injected the protamine zinc insulin through the first one left in situ. Campbell [4] advised "using three-quarter inch needles and two syringes. A needle is attached to the syringe containing regular insulin, plunged far, but not deeply, under the skin and the contents injected; the needle is almost withdrawn, its direction changed, and again inserted to a point some distance from the original injection; the empty syringe is now removed, a syringe containing protamine zinc insulin substituted and its contents injected."

These complicated methods are hardly suitable for use by the patients themselves. Furthermore, the degree of intermingling of the two insulins, either in the syringe or in the tissues is highly uncertain. Unpredictable therapeutic results must be expected. It seemed to me better to insure thorough mixture before injection and to determine what proportion of one

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form of insulin to the other would be comparable in results to separate injections.

The use of mixtures is generally believed to fail for two stated reasons: (1) Commercial solutions of protamine zinc insulin contain an excess of

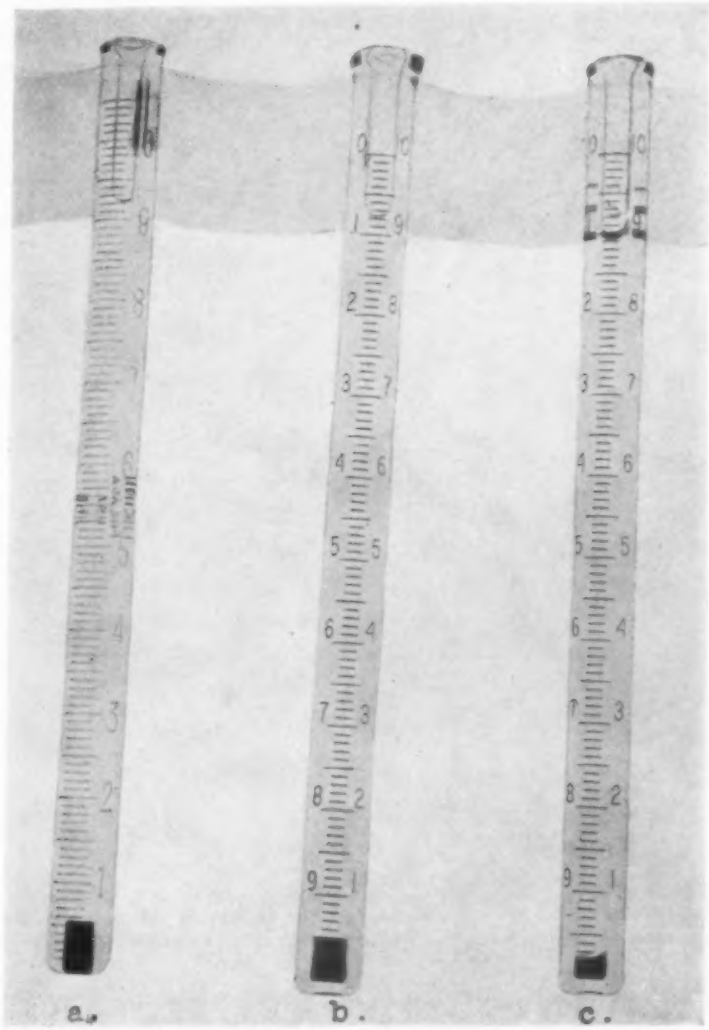

FIG. 1. Precipitate after centrifuging: (*a*) Solution of protamine zinc insulin U–40; (*b*) Mixture of equal parts of standard and protamine zinc insulin U–40; (*c*) Dilution of protamine zinc insulin U–40 with an equal amount of physiologic saline.

protamine; hence, added standard insulin will combine with the excess of protamine to form more protamine zinc insulin. (2) The activity of mixtures can not be predicted because of the uncertainty of the changes taking place in them. The first of these objections may be valid for certain pro-

portions in the mixtures, but the combining power of the excess protamine is not unlimited. By the addition of sufficiently large amounts of uncombined insulin a point is reached beyond which some of it may be expected to remain free. The clinical experiments to be reported show that the second objection applies not only to the mixtures but also to the use of separate injections.

According to Dr. F. B. Peck [5] the protamine zinc insulin made by his company contains 1.25 mg. protamine per 100 units insulin, and the excess

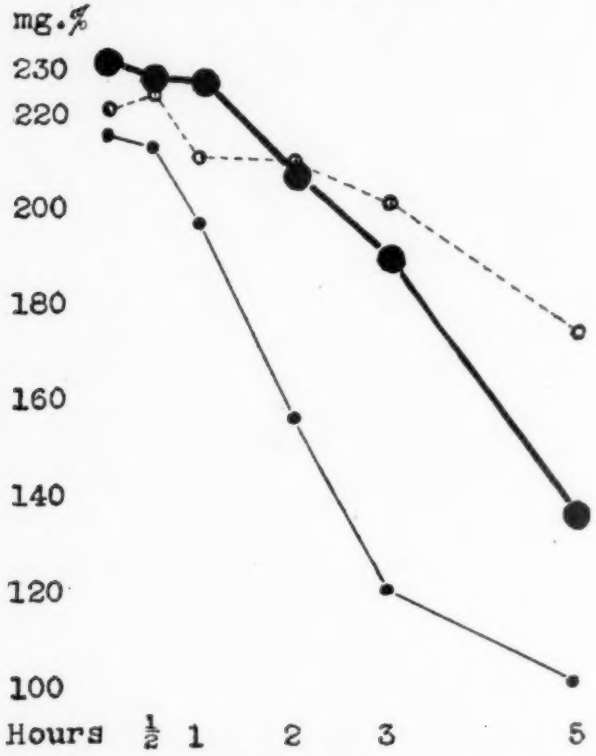

CHART 1. *Heavy line:* 1 c.c. (40 units) mixture *A* (equal parts standard and protamine zinc insulins). *Light line:* 28 units protamine zinc insulin in one arm, 12 units standard insulin in the other. *Broken line:* 40 units protamine zinc insulin.

of protamine, although not uniform in all lots, is about 40 per cent. Mixtures of equal parts of standard insulin U–40 and protamine zinc insulin U–40, therefore, should contain 28 units protamine zinc insulin and 12 units uncombined insulin in each cubic centimeter, provided that the excess of protamine combines with a quantitatively proportional amount of the added free insulin. This, of course, is a highly speculative assumption. "The union of protamine and insulin," as Dr. W. R. Campbell [6] has expressed it, "is not at all the simple one called to mind by the term 'protamine insulinate' but a very complex one."

Clinical experimentation was undertaken to determine if mixtures possess a reasonable degree of clinical predictability and usefulness despite their chemical uncertainty. To establish their practical value it must be shown that they have an early action greater than that of protamine zinc insulin and a prolonged action greater than that of standard insulin. Two sets of

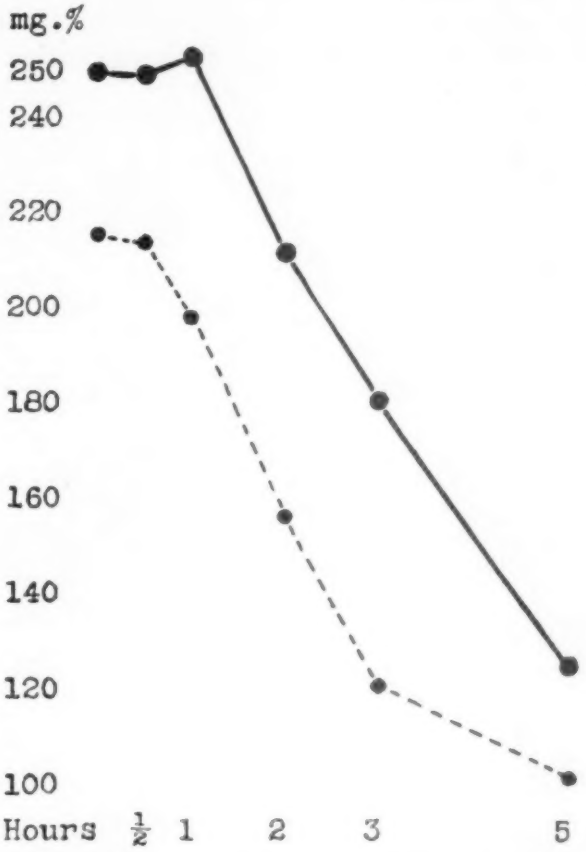

CHART 2. *Solid line:* 1 c.c. (40 units) mixture *B* (3 parts standard insulin, 2 parts protamine zinc insulin). *Broken line:* 28 units protamine zinc insulin in one arm, 12 units standard insulin in the other.

experiments were planned for the purpose. The first consisted of estimations of the blood sugar before, and half an hour, one, three, and five hours after patients with diabetes had been injected with different mixtures of the two forms of insulin. The results were compared with those obtained after injections of protamine zinc insulin alone, and of 28 units protamine zinc insulin and 12 units uncombined insulin given in separate sites. The patients fasted after the evening meal of the previous day until the tests were completed. Ten tests were made on different patients with each method.

Comparison of the curves in chart 1, each representing the mean values of 10 tests, demonstrates that the immediate action of a mixture of equal parts of protamine zinc and standard insulin is less than that of the separate injections but greater than that of protamine zinc insulin alone. A mixture of three parts standard insulin and two parts protamine zinc insulin was then tried in an effort to get greater early action. The results obtained with this mixture, shown in chart 2, are roughly parallel to those produced by separate injections, although the latter appear to act somewhat more quickly.

To determine the predictability of action of the mixtures, two lots of the

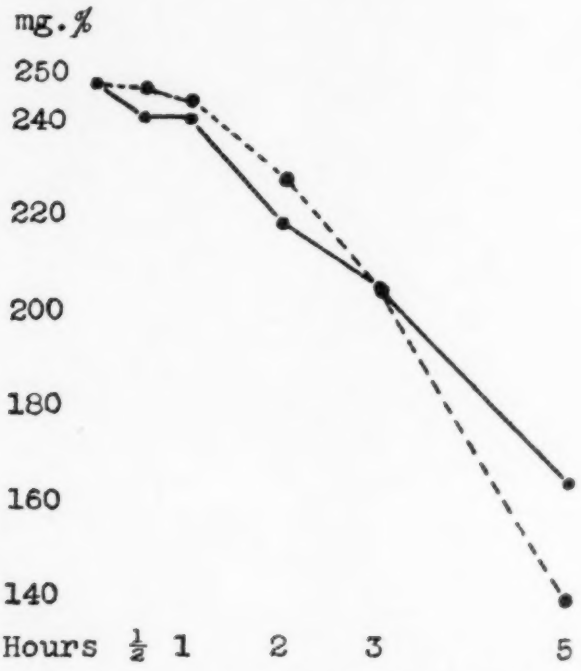

CHART 3. Comparison of results obtained with two lots of mixture A (equal parts standard and protamine zinc insulins) to show degree of predictability of action. Curves are arbitrarily started at the same initial level.

1 : 1 mixture, made from different vials of the two forms of insulin, were used, each for five of the 10 tests made with this mixture. By comparing the curves in chart 3, representing the mean values obtained in these two groups of five tests, it will be seen that the results are surprisingly similar. That is, a fair degree of predictability and uniformity of action of the mixtures is indicated. Another evidence of reasonable predictability of action is illustrated in charts 4, 5, and 6. In charts 4 and 6 the 10 individual curves obtained with the two experimental mixtures (1 : 1 and 3 : 2) are plotted separately (beginning at the same initial level), and the scatter (predictability) is compared with the spread of curves obtained with separate

injections of the two insulins (chart 5). Although there is a rather wide divergence in the responses in each group, the scatter is even greater with separate injections (chart 5) than it is with the mixtures (charts 4 and 6). In other words, predictability is at least as good with the mixtures as it is when the two forms of insulin are given separately. The difference in the responses in each group is probably the result of variation in the response

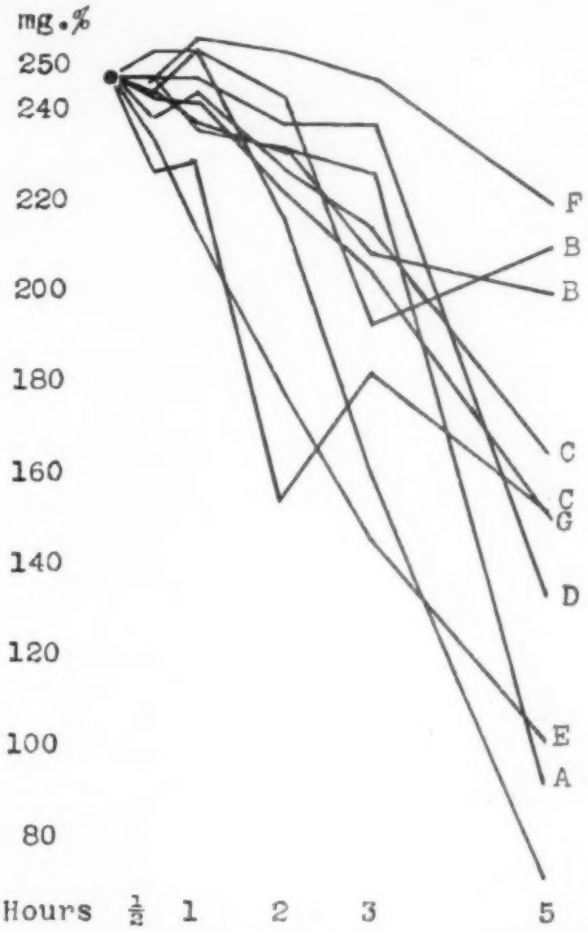

CHART 4. Scatter (predictability) after injection of 1 c.c. (40 units) mixture *A* (1:1).

of different patients to insulin. This is substantiated by comparing the curves derived from experiments with the same patients and labeled with the same letters in charts 4 and 5. Patients A and E were very sensitive to insulin; patient B was much less so.

The results of this first set of experiments indicate that, with patients in the fasting state, appropriate mixtures of standard and protamine zinc

insulins have an immediate action similar to but slightly less rapid than that of separate injections, but much more pronounced than that of protamine zinc insulin alone; also, predictability of action is as good with the mixtures as it is with separate injections.

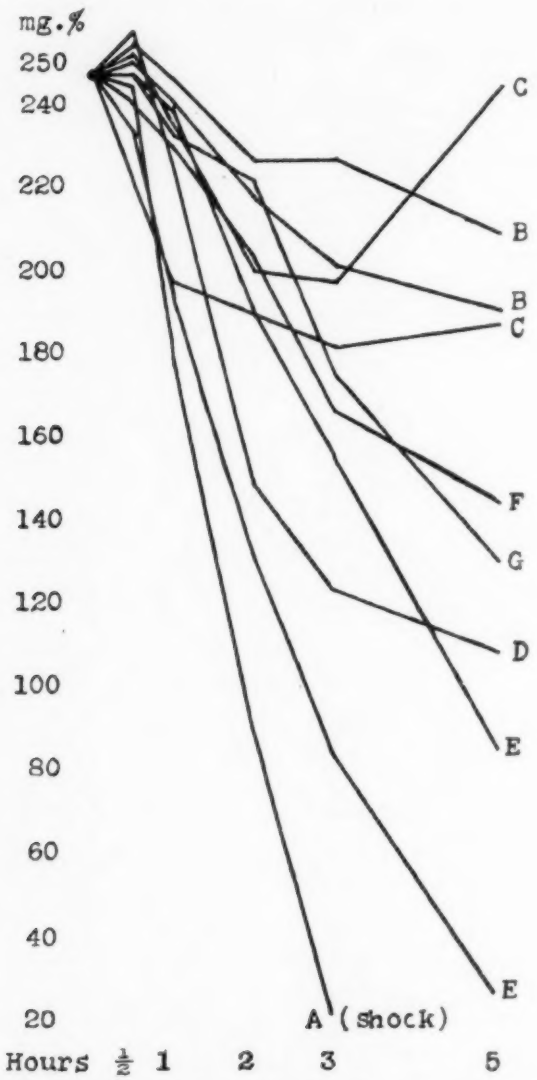

CHART 5. Scatter (predictability) after injection of 28 units protamine zinc insulin in one arm, 12 units standard insulin in the other.

In the second phase of the study the degree of prolonged action, with patients taking food, was determined. For this purpose the insulin (always a total amount of 40 units, regardless of which method was used) was in-

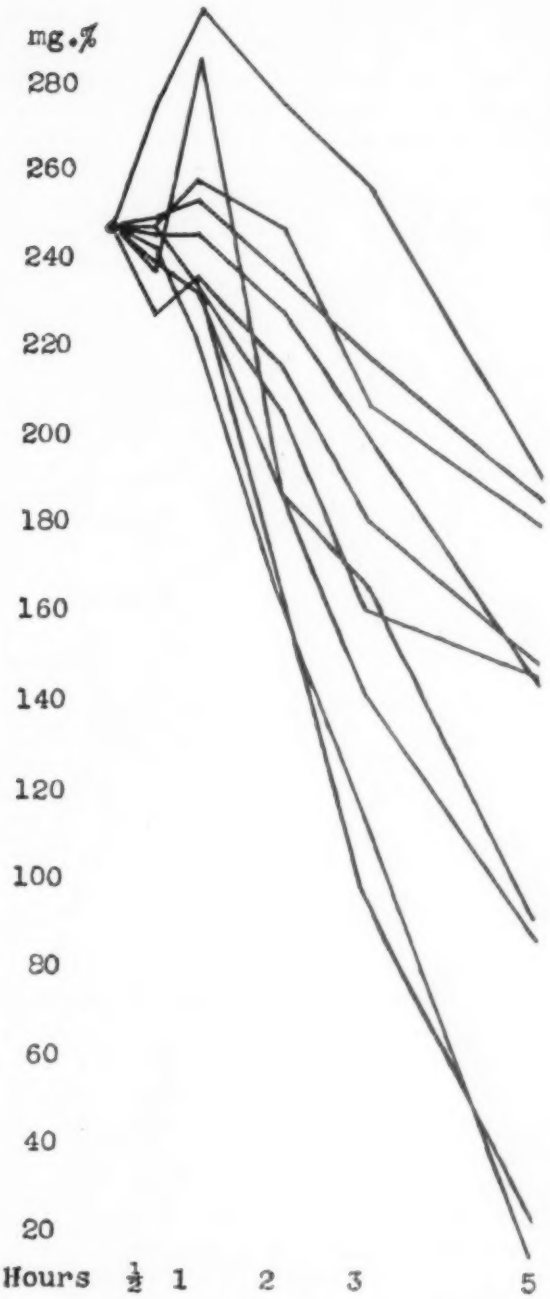

CHART 6. Scatter (predictability) after injection of 1 c.c. (40 units) mixture *B* (3 parts standard and 2 parts protamine zinc insulin).

jected at 7 a.m. Meals were given at 7:30 a.m., 12:30, and 5:30 p.m. Blood for examination was taken half an hour before and an hour after each meal, also at 10 p.m. and at 7 and 8:30 the following morning, with a second equal amount of insulin at 7 a.m. on that day. The intake of food at the four meals of the test periods was the same in all instances: breakfast, carbohydrate 41 gm., protein 10 gm., fat 23 gm., calories 411; dinner, carbohydrate 43 gm., protein 33 gm., fat 29 gm., calories 565; supper, carbohydrate 47 gm., protein 16 gm., fat 24 gm., calories 468.

The curves on charts 7 to 11, each of which represents the mean values obtained in 10 tests, illustrate the results that were obtained. With pro-

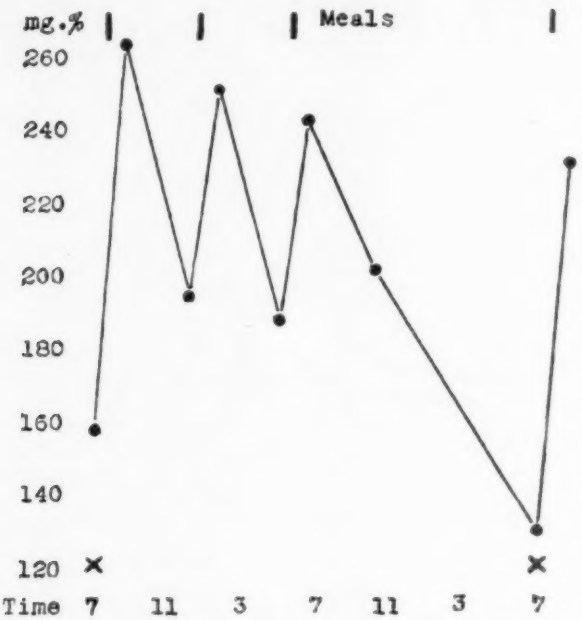

CHART 7. 40 units protamine zinc insulin at seven each morning (*X*).

tamine zinc insulin alone, marked and somewhat uniform hyperglycemia occurred after each meal. When the two insulins were given separately (28 units protamine zinc insulin in one arm, 12 units standard in the other), the rise after breakfast was largely avoided, but a high level of the blood sugar occurred toward evening, evidently because the standard insulin had spent itself at that time, and the protamine zinc insulin had not yet reached the period of its greatest activity. Increasing the amount of either would not be safe; with a larger dose of standard insulin hypoglycemia might occur before noon, with more protamine zinc insulin the dangerous time would come in the early hours of the morning.

Results with the mixtures were less promising under the conditions of this part of the study than they were with fasting patients. The hyper-

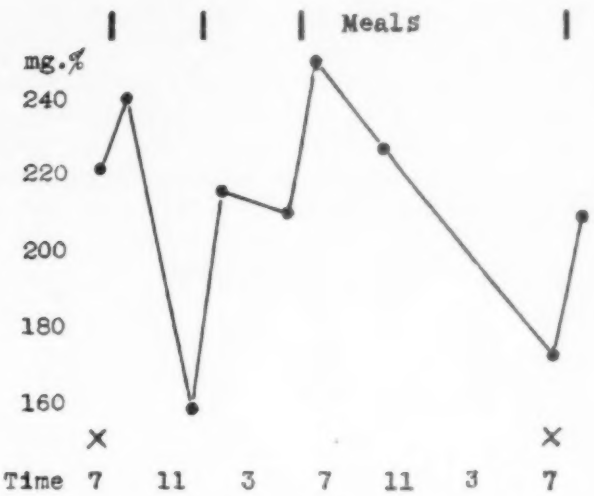

CHART 8. 28 units protamine zinc insulin in one arm, 12 units standard insulin in the other, at seven each morning (*X*).

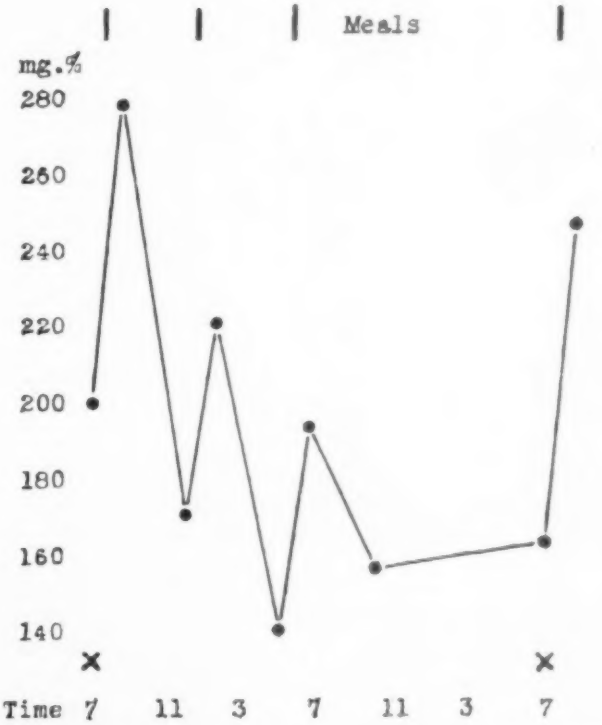

CHART 9. 1 c.c. (40 units) mixture *B* (3 parts standard insulin, 2 parts protamine zinc insulin) at seven each morning (*X*).

glycemia after breakfast was less well controlled than it was with separate injections, although it was slightly less marked than that occurring with protamine zinc insulin alone. Mixture B, consisting of three parts standard and two parts protamine zinc insulin, gave the most encouraging results, with a slightly smaller elevation of the blood sugar after meals and, after the initial rise in the morning, a somewhat more uniform level of glycemia throughout the day. Increasing the proportion of standard insulin in the

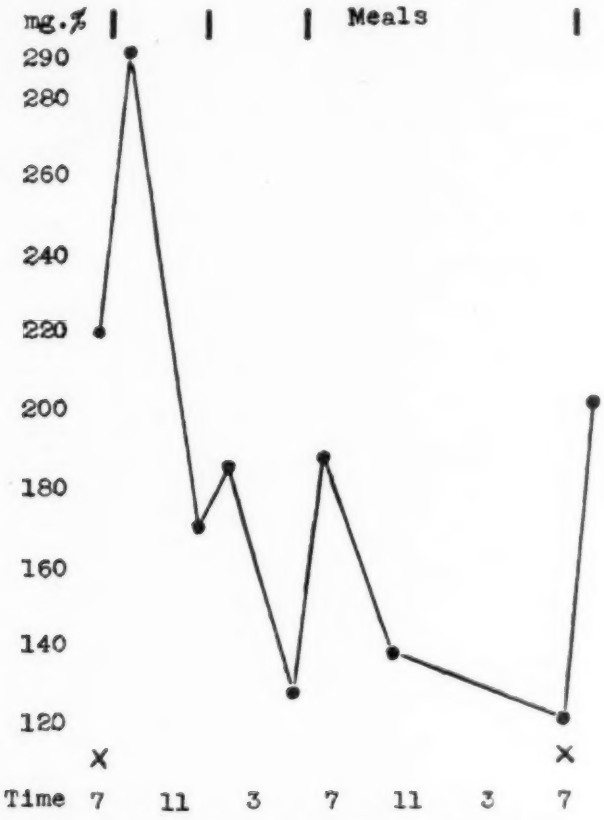

CHART 10. 1 c.c. (40 units) mixture *C* (2 parts standard insulin, 1 part protamine zinc insulin) at seven each morning (*X*).

mixtures, contrary to expectation, had only a slight effect in lessening the degree of hyperglycemia occurring immediately after breakfast, although the initial rise was followed very quickly by a marked depression of the blood sugar before noon. This was especially noticed in experiments with mixture D, consisting of three parts standard insulin and one part protamine zinc insulin (chart 11), in which the mean level of glycemia in the 10 cases of this group declined from 338 mg. to 128 mg. within three and a half hours. This remarkable result seemed to indicate that the uncombined

portion of insulin in the mixture, although present in a relatively large amount, did not act as quickly as the standard insulin that was injected separately; but its action was much prompter than that of protamine zinc insulin. Attention has previously been called to the similar but less pro-

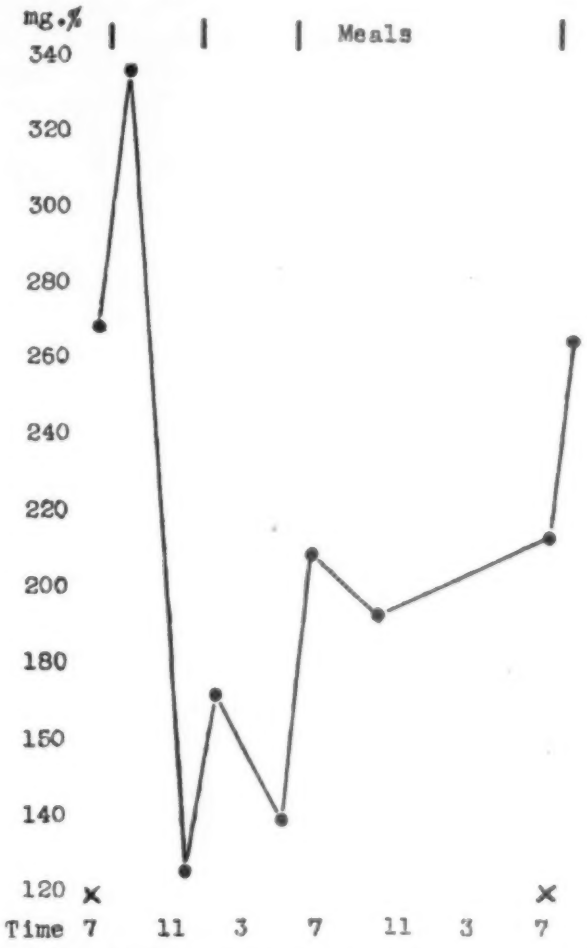

CHART 11. 1 c.c. (40 units) mixture *D* (3 parts standard insulin, 1 part protamine zinc insulin) at seven each morning (*X*).

nounced results obtained in the experiments with fasting patients (charts 1 and 2).

In an endeavor to find an explanation of this phenomenon, some of the mixture was centrifuged, and the clear supernate was injected in a patient with diabetes who was particularly sensitive to insulin (curves A in charts 4 and 5). As indicated in chart 12, the clear supernatant fluid did not contain insulin at all. All of the added standard insulin had apparently

been precipitated. This is confirmed by the fact that centrifuging equal amounts of 1:1 mixture and of plain solution of protamine zinc insulin yielded equal amounts of precipitate, whereas a comparable dilution with water or physiologic saline yielded only about half as much (figure 1). Yet the clinical results obtained with various mixtures (illustrated in charts 9, 10, and 11) differed materially from those obtained with protamine zinc insulin alone (chart 7). The immediate response with the former was much greater and indicated that much of the added standard insulin had not combined, at least not firmly, with protamine, but was present in a more readily available form.

The explanation is to be found in changes in the hydrogen ion concentration. Standard solutions of insulin are strongly acid in reaction (pH 2.5–4), whereas solutions of protamine zinc insulin have a pH of 7–8. In

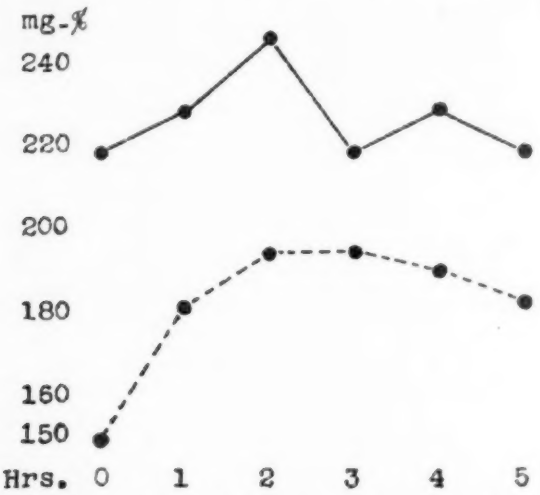

CHART 12. Curves showing absence of action of supernatant fluid obtained after centrifuging mixture *B* (broken line) and mixture *C* (solid line), in a patient who was particularly sensitive to insulin (Curves *A* in charts 4 and 5).

the mixtures the protamine apparently acts as a buffer, because in mixtures of equal parts of the two forms of insulin the hydrogen ion concentration is not half way between those of the constituents but nearer that of protamine zinc insulin. The degree of acidity increased somewhat with the amount of standard insulin in the mixtures.

The isoelectric point of insulin is about pH 5, so that at or near this level of hydrogen ion concentration it is precipitated. A study of charts 7 to 11 shows that the precipitated insulin, although not combined with protamine, had a slightly slower action than insulin in solution, but its action was much more rapid than that of protamine zinc insulin.

As a result of this finding, another experiment was carried out in which the standard solution of insulin was alkalinized to a reaction approximately

equal to that of the protamine zinc insulin before the two solutions were mixed. It was done by adding 0.12 c.c. of twentieth normal solution of sodium hydroxide to 5 c.c. of standard insulin. During the addition of the alkali a precipitate was formed which redissolved when the whole amount of alkali had been added. Clinical results with the alkalinized mixtures were not better than those obtained with the plain combinations, and there was some evidence that they deteriorated with time. Further study in this direction, therefore, was abandoned.

Summary

Experiments are recorded which indicate that mixtures of standard and protamine zinc insulin are suitable for clinical use. The claim that the results with such mixtures are wholly unpredictable is not supported by these experiments. Predictability is at least as good as it is with separate injections of the two forms of insulin. A mixture of three parts of standard insulin and two parts of protamine zinc insulin gave the most promising results. The use of such a mixture may be advantageous in the treatment of certain suitable patients who require injections of standard insulin as a supplement to treatment with protamine zinc insulin. Moreover, they may be preferable to the use of protamine zinc insulin alone when it does not prevent marked post-prandial periods of hyperglycemia.

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SUBACUTE STAPHYLOCOCCUS ENDOCARDITIS AND STAPHYLOCOCCUS BACTEREMIA WITHOUT ENDOCARDITIS WITH A REPORT OF THE FAVORABLE EFFECT OF SULFANILAMIDE AND SULFATHIAZOLE IN TWO CASES *

By HAMILTON SOUTHWORTH, M.D., *New York, N. Y.*

THE staphylococcus is not an uncommon invader of the human blood stream but cases of prolonged bacteremia without an obvious focus of infection are rare. In most instances an obvious portal of entry is present and the bacteremia is either a temporary one at the height of the local infection or a septicemia with a stormy course. Low-grade bacteremias of long duration do, however, occur, and in such cases the question of a subacute or chronic endocarditis is invariably raised.

Searching for such case reports, with or without endocarditis, in the literature, we were able to find only those that have been listed in table 1.[1, 2, 3, 4, 5, 6] All cases in which there was a proved focus (osteomyelitis,

TABLE I

Author	Organism	Endocarditis at Autopsy	Clinical Duration	First Positive Culture
Thayer	*Staph. aureus*	+	5–6 months	No culture taken
Stich	*Staph. albus*	+	5½ months	About 4 wks. before death
Le Clerc	*Staph. albus*	No autopsy	8–9 months	2 months before death
Young	*Staph. albus*	No autopsy	11 months	10 months before death
Lemierre et al.	*Staph. aureus*	+	14 months	2 months before death
Horder	*Staph. albus*	+	24–30 months	——

urinary tract infection, etc.) have been excluded,† as well as those which lacked evidence, at least of a clinical nature, that the bacteremia was of over five months' duration.

It is to be noted that all these cases presumably had endocarditis. All of the cases ended fatally, and in each of the four instances in which autopsy was performed an intracardiac vegetation was found. In four the staphylococcus involved was described as an albus and in two as an aureus. No further bacteriologic study was made. In only one instance was the organism obtained from the blood stream more than two months before death.

To this list we would like to add two cases from the Presbyterian Hospital in New York City.

* Received for publication August 10, 1940.

From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and The Presbyterian Hospital, New York City.

† Horder's case has been included even though there is no mention whether or not there was a focus other than on the heart valves.

Case 1. R. M., a 33-year-old social worker, was first admitted to the Presbyterian Hospital in March 1937. At the age of nine she was told she had congenital heart disease. In September 1935 she had been admitted to another hospital with a history of four days of pleurisy which was confirmed by roentgen-ray. In addition to the signs of a congenital heart lesion, two petechiae were noticed, and a *Staphylococcus aureus* was obtained from the blood stream. Her fever subsided and she was able to return to work. But in November 1935 an abscess of the buttock necessitated readmission and this was followed by a recurrence of pain in the chest and of fever and then by an abscess near the other hip. In March 1936 she became aware of nightly fever (101°–102°), cough, night-sweats, and a weight loss of 12 pounds. In October 1936 she was again admitted with an acute pulmonary infection and repeated blood cultures grew out a *Staphylococcus aureus*. The diagnosis of bacterial endocarditis was made. In December 1936 she spent four weeks in another hospital because of fever, sweats and cough. The diagnosis of subacute bacterial endocarditis was thought probable, though blood cultures remained negative.

On admission to the Presbyterian Hospital the patient had an enlarged heart with signs typical of a patent ductus arteriosus. The spleen extended 2 cm. below the costal margin but no petechiae were observed. It was noted that she looked tired rather than seriously ill. Her hemoglobin was 79 per cent, red blood cells 3,800,000, white blood cells 7,600, and differential count normal. The sedimentation rate (Westegren) was 76 mm./1 hour. Urinalysis was normal; the blood Wassermann test was negative. Five successive blood cultures each grew out a *Staphylococcus albus*. This was studied by Dr. Richard Thompson and found to be a typical Group C non-pathogen, mannitol and coagulase negative.[6] A thorough search for a focus of infection (which included roentgen-rays of sinuses, mastoids, teeth, lungs, and skeleton; cultures of urine and of irrigations of antra and sphenoid; and gall-bladder and gastrointestinal series) was entirely fruitless. The patient showed fever only intermittently.

She was placed on sulfanilamide, receiving 3.6 gm. daily for two weeks and attaining a blood level of 4 mg. per cent of the free drug. Thereafter five blood cultures all remained sterile and she went home symptom-free, the consensus of medical opinion being that she had had a bacteremia without endocarditis.

Three months later, however, fever recurred and staphylococci were again obtained by blood culture. The patient was readmitted for more sulfanilamide but developed fever and rash so that the drug had to be stopped after four days without therapeutic effect. Cardiac insufficiency then set in with a rise in venous pressure to 180 mm. of saline, and in spite of treatment the patient died in September 1937, a death of cardiac failure, not of sepsis.

Autopsy, unfortunately limited to the heart and lungs, revealed no endocarditis and no origin for the bacteremia. The heart was slightly enlarged, a patent ductus arteriosus was present, and there was evidence of chronic passive congestion.

Case 2. M. B., a 70-year-old secretary, was admitted in November 1938. Twenty-five years previously he had been told he had an organic heart murmur but he remembered no symptoms suggestive of rheumatic fever. In May 1938 he first became ill with fever, malaise, and night-sweats. Shortly thereafter he developed tender, red, painful areas successively in the neck, the hip, both arms, and finally in the fingers and toes. All of these were of brief duration and subsided without suppuration. In September 1938 he was in the Johns Hopkins Hospital under the care of Dr. Louis Hamburger. A probable diagnosis of subacute bacterial endocarditis was made, but by blood culture nothing was obtained save a *Staphylococcus albus* which appeared only once on a plate and once in a flask and was therefore considered a contaminant. During the next two months the patient was able to work part time and fever occurred only intermittently in association with recurrences of what appeared to be metastatic infective foci, usually in the extremities.

On admission the patient was chronically but not severely ill. The heart seemed slightly enlarged and there was a systolic murmur of moderate intensity at the apex. The liver edge extended 3 cm. below the costal margin and a firm splenic tip was just palpable. Hemoglobin was 11.2 gm. (77 per cent), red blood cells 4,030,000, white blood cells 10,250 with 81 per cent polymorphonuclear leukocytes. Urinalysis was negative. The sedimentation rate (Westegren) was 52 mm./1 hour. Two blood cultures grew out *Staphylococcus albus* in both flasks. A thorough search for a focus of infection (roentgen-rays of teeth, lungs, genito-urinary tract, gastrointestinal tract and gall-bladder) proved negative. The patient refused chemotherapy and went home with a probable diagnosis of subacute staphylococcal endocarditis. Dr. Richard Thompson studied the organism and found it to give a lemon growth, to be antigenically a group C, but to show evidences of pathogenicity in that it fermented mannitol and produced coagulase.[6]

During the next year the patient continued at intervals to run fever to 101° or 102°. At first these febrile episodes were nearly always accompanied by the development of a non-suppurating peripheral area of infection; later the fever occurred more frequently without obvious metastatic focus. Between bouts the patient felt well and carried on his usual work. In fact, after a period of low morale in February 1939, he even gained in weight. No petechiae were observed and the spleen did not increase in size. It was noticeable, however, that the systolic murmur grew progressively louder and this in spite of the fact that there was no increase in anemia. In October 1939 blood cultures taken during an afebrile interlude, again grew out a *Staphylococcus albus* in both flasks.

In January 1940 a supply of sulfathiazole was obtained through the kindness of Dr. George Harrop of E. R. Squibb and Sons, and the patient consented to take it. It was then found that the patient had gained 15 pounds in 14 months and that his hemoglobin had risen to 14.0 gm. (98 per cent) with 4,850,000 red blood cells and 6,850 white blood cells and a normal differential count. But on blood culture *Staphylococcus albus* was still obtained and the sedimentation rate was 59 mm./1 hour. Sulfathiazole was then begun in increasing doses until a blood level of 13.5 mg. of free and 16.0 of total drug was obtained. In 10 days a total of 41.25 gm. was administered. At the end of this time fever, a macular rash, and a sudden drop in the percentage of granulocytes to 39 per cent with the appearance of 3 per cent of myelocytes caused its discontinuance. In seven days all of these findings had disappeared. The hemoglobin fell gradually from 14.0 to 12.8 gm. but the total leukocytes did not vary significantly. The only urinary changes occurred during the week after the sulfathiazole was stopped and consisted of a transitory faint trace of albumin and a rare red blood cell and hyaline cast in the centrifuged sediment.

After 10 grams of sulfathiazole had been administered, blood cultures, for the first time in 17 months, remained sterile. At the end of the course of chemotherapy and one week later there was still no growth. Since that time 12 months have elapsed and the patient has been entirely free of fever and metastatic infection. He has continued to gain in strength and weight. Two more blood cultures have remained sterile. The heart murmur has increased slightly but the spleen has receded until it is no longer palpable. The sedimentation rate on January 14, 1941, had fallen to 7 mm./hour.

The two cases here reported illustrate the extreme difficulty of differentiating without an autopsy subacute endocarditis from subacute bacteremia without endocarditis when caused by the staphylococcus, unless an unmistakable change occurs in a heart murmur without the development of anemia. This difficulty is increased by two factors. First, staphylococcus bacteremia is well known for its ability to cause metastatic abscesses and splenomegaly.

And second, as pointed out by Thayer,[8] only about 20 per cent of staphylococcus endocarditis cases ever have petechial hemorrhages.

In both of our cases, endocarditis was suspected. The first, with its congenital anomaly, the recurrence of bacteremia after chemotherapy, the story of petechiae at another hospital, and the unexplained rapidity of the terminal cardiac insufficiency, was certainly very suggestive, and yet, at autopsy, no vegetations were found. In the second case the increase in the heart murmur and the initially painful fingers and toes suggested endocarditis, but the exceedingly low-grade course and the effectiveness to date of chemotherapy may be evidence against it.

Summary

1. Two cases are reported of prolonged (over five months) staphylococcus bacteremia without an obvious focus of infection other than possibly an endocarditis. Six similar instances have been gathered from the literature.

2. In one case staphylococci were consistently present in the blood stream for 17 months and yet the patient maintained relatively good health.

3. In both cases the staphylococcus was antigenically a group C organism.

4. The difficulty of determining without autopsy whether or not there really is an endocarditis is stressed.

5. The favorable influence in one case of sulfanilamide and in another of sulfathiazole is described.

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TREATMENT OF PNEUMOCOCCIC PNEUMONIAS WITH SULFAPYRIDINE, SULFATHIAZOLE AND SERUM; ANALYSIS OF THE RESULTS OF SPECIFIC THERAPY AT THE BOSTON CITY HOSPITAL FROM JULY 1939 THROUGH JUNE 1940 *

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The present report deals with the results of specific therapy in the pneumococcic pneumonias of adults at the Boston City Hospital during the second year in which effective chemicals were available. In the preceding year,[1] specific serums and sulfapyridine each were used separately in a large proportion of the cases, and the results of treatment with each of these agents were quite comparable. The combination of serum and sulfapyridine was used during that year in some of the most severe cases, while a considerable proportion of the cases received neither of these remedies. During the year covered in the present report (July 1939 through June 1940), sulfapyridine therapy was started, in general, as soon as the diagnosis of pneumonia was made, and serum was given, in addition, to some of the most severe cases and to those in whom the drug either occasioned excessive discomfort or failed to bring about an adequate clinical response. Beginning February 1, sulfathiazole was substituted for sulfapyridine and used in identically the same manner on four of 12 medical wards. As in previous studies, all cases with clinical, roentgenographic or autopsy findings of pneumonia associated with the identification of pneumococci are included for analysis. The proportion of patients who failed to receive any specific treatment was much smaller than in the previous year.

Analysis of Cases and Results of Therapy

The distribution of cases according to the type of pneumococcus and the kind of specific therapy used is shown in table 1. Of the 911 cases, 691, or 76 per cent, were treated with either sulfapyridine, sulfathiazole or serum, or with a combination of serum and one of the two drugs. Among these 691 specifically treated cases there were 113 deaths, a mortality of 16.4 per cent. In the previous year, only 54 per cent of all the pneumococcic pneumonias received sulfapyridine or serum, or both, and the mortality among the cases so treated was 17.5 per cent. During the present year, serum was used, for the most part, to supplement drug therapy in some of the severe cases due to the common Types I, II, V, VII and VIII. More than one-

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TABLE I

Distribution of Cases and Deaths According to Pneumococcus Types
Boston City Hospital, July 1, 1939–June 30, 1940

Type	Sulfapyridine		Sulfathiazole		Sulfapyridine and Serum		Sulfathiazole and Serum		No Specific Therapy			All Cases	
	No.	Died	No.	Died	No.	Died	No.	Died	No.	Died§		No.	Died
I	71^{16}	6^{4}	26^{5}	1^{1}	28^{11}	4^{3}	8^{3}	1^{1}	11^{3}	4^{3}	(4)	147^{38*}	16^{12}
II	32^{7}	3^{2}	9^{3}	1	10^{9}	3^{3}	2^{2}	0	4	2	(2)	66^{20}	9^{6}
III	73^{10}	19^{8}	14	2	0	—	1^{1}	1^{1}	34^{1}	14^{1}	(8)	122^{12}	36^{8}
IV	13^{4}	1	5	1	1	0	0	—	7^{2}	3^{2}	(3)	26^{6}	5^{2}
V	30^{7}	2^{2}	14^{3}	0	8^{6}	0	1^{1}	1^{1}	5^{1}	3^{1}	(3)	58^{18}	6^{4}
VI	18^{1}	1	5	1	0	—	0	—	12^{1}	6^{1}	(4)	35^{2}	8^{1}
VII	33^{4}	2	17^{3}	1	9^{6}	4^{4}	2^{2}	1^{1}	5^{1}	1^{1}	(1)	66^{15}	9^{6}
VIII	35^{7}	5^{3}	12^{3}	0	4^{3}	0	1^{1}	0	9^{2}	7^{2}	(3)	62^{16}†	13^{5}
IX	7	1	1	0	0	—	0	—	7	4	(3)	15	5
X	5	1	2	0	1	0	1	1	3^{1}	3^{1}	(2)	12^{1}	5^{1}
XI	6	0	1	0	0	—	0	—	11^{1}	6^{1}	(4)	18^{1}	6^{1}
XII	8^{1}	1	3^{1}	0	0	—	0	—	5^{1}	2^{1}	(2)	16^{2}	3^{1}
XIII	9	4	5	3	0	—	0	—	9^{1}	8^{1}	(5)	23^{1}	15^{1}
XIV	14^{3}	5^{2}	7^{1}	0	1^{1}	1^{1}	0	—	7^{2}	4^{2}	(2)	29^{7}	10^{5}
XV	8	1	1	0	0	—	0	—	6	4	(2)	15	5
XVI	6^{1}	3	1	0	0	—	0	—	2	0		9^{1}	3
XVII	11	3	1	0	0	—	0	—	8^{1}	5^{1}	(3)	20^{1}	8^{1}
XVIII	15^{2}	5	4^{1}	0	1^{1}	0	0	—	15	7	(7)	35^{4}	12
XIX	18	4	5	1	0	—	0	—	11	5	(4)	34	10
XX	3	1	3	0	0	—	0	—	12^{3}	6^{3}	(4)	18^{3}	7^{3}
XXI	2	1	1	0	0	—	0	—	4	2	(2)	7	3
XXII	0	—	3	1	0	—	0	—	1	1		4	2
XXIII	3	0	0	—	0	—	0	—	2	1	(1)	5	1
XXIV	3	1	1	0	0	—	0	—	3	1	(1)	7	2
XXV	8^{2}	3^{2}	2	1	0	—	0	—	3^{1}	2^{1}	(2)	13^{4}	6^{3}
XXVII	0	—	0	—	0	—	0	—	1	0		1	0
XVIII	6	1	3	1	0	—	0	—	7^{1}	4^{1}	(3)	16^{1}	6^{1}
XXIX	4	2	4	1	0	—	0	—	9^{1}	4^{1}	(4)	17^{1}	7^{1}
XXXI	0	—	1	1	0	—	0	—	4	0		5	1
XXXII	0	—	0	—	0	—	0	—	1	0		1	0
Not I–XXXII	5^{3}	3^{3}	2	0	0	—	0	—	2	0		9^{3}	3^{3}
Total	446^{89}	79^{34}	153^{18}	16^{1}	72^{37}	12^{11}	16^{10}	5^{4}	220^{24}	109^{24}	(79)	911^{188}‡	222^{64}
Per cent Died	17.7		10.5		16.7		31.3		49.5			24.4	

Superscripts represent numbers of cases in which pneumococci were cultured from the blood.

* Three patients received serum alone, no deaths; † 1 received serum alone and died.

‡ Includes 4 serum treated cases.

§ Parentheses enclose numbers of cases typed after death.

half of the 88 patients who received the combined treatment had positive blood cultures and 17 of them died, a mortality of 19.3 per cent. The mortality among the patients who received no specific therapy (except sulfanilamide in a few instances) was very high (49.5 per cent). In more than three-fourths of the fatal cases of this group, however, the etiological diagnosis, and usually the anatomical diagnosis as well, was first made at autopsy. Most of these patients, as will be seen later (tables 2 and 3), were being treated primarily for other serious illnesses, of themselves highly fatal.

The occurrence of some of the more important prognostic factors and their effect on the mortality are shown in table 2. The gross mortality in the 518 patients who were treated with sulfapyridine, alone or with serum, was 17.4 per cent, as compared with a death rate of 12.4 per cent among the 169 cases who received sulfathiazole, with or without serum. These two groups of cases were quite comparable with respect to all the factors listed in the table with one important exception, namely, with respect to the

TABLE II

Analysis of Incidence of Important Prognostic Factors in Cases of Pneumococcic Pneumonia and Their Effect on Mortality

Prognostic Factor	Sulfapyridine Alone or with Serum				Sulfathiazole Alone or with Serum				No Specific Therapy				All Cases*			
	Number	Died	Per cent Died	Incidence, per cent	Number	Died	Per cent Died	Incidence, per cent	Number	Died	Per cent Died	Incidence, per cent	Number	Died	Per cent Died	Incidence, per cent
Result of blood culture																
Positive†	106	35	33	21	28	5	18	17	24	24	100	13	158	64	41	18
Negative	405	53	13	79	141	16	11	83	159	75	47	87	708	144	20	82
Not done	7	3	—		0	—	—		37	10	27		45	14	31	
Age (years)																
Less than 20	35	2	6	7	20	0	0	12	12	1	8	5	67	3	4	7
20–39	157	11	7	30	46	3	7	27	50	9	18	23	254	23	10	28
40–59	183	29	16	35	81	11	14	48	68	31	46	31	334	71	21	37
60 and older	143	49	34	28	22	7	32	13	90	68	74	41	256	125	49	28
Lobar pneumonia	370	53	14	71	123	11	9	73	31	11	35	14	527	75	14	58
Atypical (broncho-) pneumonia	148	38	26	29	46	10	22	27	189	98	52	86	384	147	38	42
Pneumonia: Primary	421	52	12	81	135	8	6	80	94	22	23	43	653	82	13	72
"Secondary"	97	39	40	19	34	13	38	20	126	87	69	57	258	140	54	28

TABLE II (*Continued*)

Prognostic Factor	Sulfapyridine Alone or with Serum				Sulfathiazole Alone or with Serum				No Specific Therapy				All Cases*			
	Number	Died	Per cent Died	Incidence, per cent	Number	Died	Per cent Died	Incidence, per cent	Number	Died	Per cent Died	Incidence, per cent	Number	Died	Per cent Died	Incidence, per cent
Extent of lesion																
Single lobe	332	37	11	64	118	10	8	70	78	15	19	35	531	62	12	58
Multiple lobes																
Unilateral	82	14	17	16	17	2	12	10	13	4	31	6	112	20	18	13
Bilateral	104	40	38	20	34	9	26	20	129	90	70	59	268	140	52	29
Day treatment begun																
First	47	9	19	9	15	0	0	9								
Second	105	12	11	20	28	1	4	17								
Third	79	6	8	15	31	5	16	18								
Fourth	81	11	14	16	37	5	14	22								
Fifth	76	10	13	15	14	1	7	8								
Sixth	35	3	9	7	16	2	13	9								
Seventh or later	58	19	33	11	23	4	17	14								
Not known	37	21	57	7	5	3	60	3								
Admitted: Before Feb. 1	318	48	15.1		0	—	—		138	60	43.5		460	109	23.7	
After Feb. 1	200‡	43	21.5		169	21	12.4		82	49	59.8		451	113	25.1	
Totals	518	91	17.4	100	169	21	12.4	100	220	109	49.5	100	911	222	24.4	100

* Including 4 cases treated with serum alone.

† Incidence calculated for cases in which blood cultures were made.

‡ These included 42 bacteremic cases (incidence 21%) with 20 deaths (mortality 48%). There were 33 who received serum in addition to drug with 9 deaths (27%).

age distribution. More than one-half of the deaths among the sulfapyridine treated cases occurred in patients over 60 years of age, whereas only one-third of those treated with sulfathiazole were of this age group. Since patients over 60 years of age were relatively twice as frequent among the former cases and since the mortality within each age group was essentially the same in both groups, this factor alone may account for most, if not all, of the difference in mortality between the sulfapyridine treated cases and those treated with sulfathiazole. This is further suggested by the fact that the mortality in the sulfapyridine treated cases was higher after February 1 than before that time, when all of the cases were treated with that drug.

TABLE III

Serious Antecedent Systemic Complications in Patients with "Secondary" Pneumococcic Pneumonia

Antecedent Disease	Sulfapyridine Alone or with Serum		Sulfathiazole Alone or with Serum		No Specific Therapy		All Cases	
	No.	Died	No.	Died	No.	Died	No.	Died
Congestive cardiac failure	18	10	7	2	30	23	55	35
Acute coronary occlusion	1	1	2	2	4	2	7	5
Cerebrovascular accident	3	2	2	2	17	16	22	20
Renal failure	4	1	1	1	7	7	12	9
Hepatic disease, severe	4	3	1	0	3	3	8	6
Operations or injuries:								
Head and neck	6	1	0	–	4	2	10	3
Respiratory tract	5	0	2	0	5	2	12	2
Abdomen	23	9	3	1	11	4	37	14
Others	7	2	0	–	0		7	2
Asthma, acute	8	1	4	0	6	2	18	3
Severe infections (non-pneumococcic)	11	5	7	2	15	5	33	12
Poisoning (except alcohol)	4	2	1	1	1	0	6	3
Severe anemia, blood loss	2	1	0	–	4	3	6	4
Malignant tumors:								
Lung	2	2	1	0	4	4	7	5
Others	3	1	2	1	14	13	20	16*
Acute alcoholic intoxication †	36	6	5	3	7	0	48	9
Delirium tremens †	20	4	6	0	3	0	29	4
Pregnancy or puerperium †	10	1	0	–	4	0	14	1

* Include 1 patient treated with serum alone.
† Not included as "secondary" pneumonias.

An appreciable proportion of the specifically treated cases occurred in the course of other serious illnesses, and the mortality in such "secondary" pneumonias was particularly high. This factor also accounted for the high death rate among the patients who received no specific therapy. The primary diseases, in the course of which these secondary pneumonias occurred, are listed in table 3. Of interest also are the cases complicating pregnancy and the puerperium which are listed in this table because of the high expected mortality,[2] although they are not classified as "secondary" pneumonias. The only death among these cases occurred in a patient whose

pneumonia complicated a septic abortion. The mortality among patients admitted acutely intoxicated from alcohol or who had delirium tremens in the course of their pneumonia was also comparatively low.

Dosage. Sulfapyridine and sulfathiazole were used in identically the same manner. In general, the initial dose was 2 grams followed in two hours by 1 or 2 grams and then 1 gram every four hours. The sodium salt of each was used in occasional cases where vomiting was excessive or where oral dosage was impractical. In such cases an initial dose of 4 or 5 grams, followed by 2 to 3.3 grams every eight to twelve hours were given in sterile physiological saline in concentrations of 0.5 to 5 per cent. It was rarely necessary to give more than three intravenous doses, after which oral therapy was used. The drug was usually discontinued after two to four days of normal temperature, provided the other symptoms of active infection had subsided. Fluids were given liberally, with an attempt being made to attain a daily intake of 3 to 4 liters.

TABLE IV

Dosage of Sulfapyridine and Sulfathiazole Used and the Duration of Acute Illness after Chemotherapy Was Started

	Treated with Sulfapyridine				Treated with Sulfathiazole			
	Alone		With Serum		Alone		With Serum	
	Recovered	Died	Recovered	Died	Recovered	Died	Recovered	Died
Number of Cases *	367^{45}	79^{24}	60^{28}	12^{11}	137^{17}	16^{1}	11^{6}	5^{4}
Average total dose (grams)	23	18	27	33	27	18	41	35
Bacteremic cases	31	14	30	33	27	3	56	39
Non-bacteremic cases	21	20	25	24	27	19	24	23
Number of patients * who received a total dose of:								
5 grams or less	5^{1}	13^{8}	1	0	0	2^{1}	0	0
6–10 grams	35	23^{8}	4^{3}	1^{1}	4^{1}	3	1	0
11–15 grams	60^{4}	9^{3}	7^{2}	2^{2}	10^{1}	4	0	1^{1}
16–20 grams	66^{4}	9^{4}	10^{3}	1^{1}	27^{3}	3	0	0
21–25 grams	70^{6}	7^{1}	8^{3}	3^{3}	27^{3}	2	2	1
26–30 grams	52^{11}	4	9^{5}	0	27^{3}	1	2^{1}	1^{1}
31–40 grams	59^{12}	7	8^{4}	1^{1}	30^{6}	0	2^{1}	0
41+ grams	20^{7}	7^{3}	13^{7}	4^{4}	12^{1}	1	4^{4}	2^{2}
Number of patients * whose disease terminated after:								
12 hours or less	87^{7}	10^{5}	2	0	28^{3}	2^{1}	0	0
13–24 hours	93^{11}	14^{8}	11^{5}	1^{1}	28^{6}	0	2^{1}	0
25–36 hours	80^{12}	4^{1}	19^{7}	1^{1}	31^{5}	2	3^{1}	1^{1}
37–48 hours	27^{3}	5^{1}	5^{3}	0	8^{1}	4	1	1^{1}
49–72 hours	26^{4}	8^{3}	6^{3}	1^{1}	17^{2}	1	0	0
73–96 hours	19^{3}	9^{2}	5^{2}	2^{2}	11^{1}	0	2^{1}	0
97–120 hours	12^{1}	4^{2}	3^{1}	0	4	2	0	
121 hours or longer	18^{3}	25^{2}	6^{2}	7^{6}	6	5	2^{2}	3^{3}
Indeterminate	5	—	3^{3}	0	4	0	1^{1}	0

* Superscripts represent numbers of patients with positive blood cultures.

The average total dose actually used in all cases was somewhat greater for sulfathiazole than for sulfapyridine, and doses of more than 25 grams were used in a larger proportion of cases which received the former drug, as noted in table 4. This was true both in patients treated with drug alone and in those who received serum in addition. About one-half of the fatal cases who were given only sulfapyridine, and about one-third of those who were treated with sulfathiazole alone and died, received a total of 10 grams of drug or less.

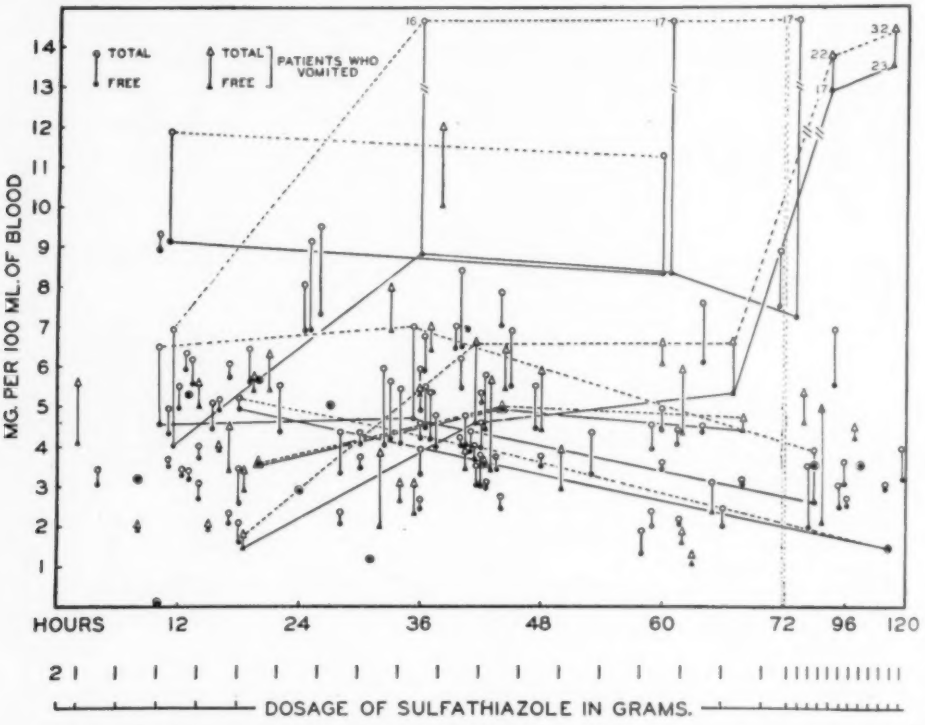

FIG. 1. Blood levels of free and total sulfathiazole in patients who received an initial dose of 2 grams, 1 gram two hours later and then 1 gram every four hours. The lines connect determinations made in the same patient.

The concentrations of sulfathiazole attained in the blood were generally lower than those found after treatment with the same dose of sulfapyridine. In most cases, the concentration of free sulfapyridine ranged between 3 and 9 mg. per cent, while the levels of free sulfathiazole ranged between 2 and 6 mg. per cent. Large amounts of acetylated drug were usually present in the blood of sulfapyridine treated cases, and constituted from 20 to 50 per cent of the total circulating drug. Only small amounts of acetylated drug were found in sulfathiazole treated cases, except in occasional patients with nitrogen retention. In figure 1 are shown the blood levels in a group of consecutive patients, all of whom received identical dosage of sulfathiazole.

This figure may be compared with a similar one previously published,[1] in which the levels on the same dose of sulfapyridine are charted in the same manner. Wide variations were noted, and these were not related to vomiting. The patients showing the highest levels of sulfathiazole all had high blood non-protein nitrogen levels at the same time.

Serum was given in divided doses, beginning with an initial injection of 1 or 2 c.c., after the usual precautions. Concentrated rabbit serums were used in almost every case. Nearly all the patients received either two or three doses, two hours apart, intravenously. Occasional patients were given part or all of the serum intramuscularly. The total amount given was 40 c.c. or less, and usually contained between 50,000 and 400,000 units. Doses greater than 200,000 units were used in 23 patients, of whom nine died. In the majority of cases, the first dose of serum was given from 12 to 36

TABLE V

Relation of Serum Administration to Drug Therapy and to the Termination of the Disease in Patients Receiving Combined Therapy

A. Interval from first dose of drug to first dose of serum					*B.* Duration of acute illness after first dose of serum				
Hours	Sulfapyridine		Sulfathiazole		Hours	Sulfapyridine		Sulfathiazole	
	Recovered	Died	Recovered	Died		Recovered	Died	Recovered	Died
12 or less	7^{2}	2^{2}	1^{1}	2^{2}	12 or less	38^{16}	3^{3}	7^{3}	1^{1}
13–24	21^{9}	4^{4}	3^{2}	2^{1}	13–24	9^{3}	—	—	—
25–36	15^{10}	1	4^{1}	—	25–36	5^{2}	—	—	—
37–48	3^{1}	1^{1}	2^{1}	—	37–48	3^{2}	1^{1}	—	1^{1}
49–72	5^{1}	2^{2}	1^{1}	—	49+	5^{4*}	8^{7}	4^{3*}	3^{2}
73+	9^{4}	2^{2}	—	1^{1}					
Total	60^{27}	12^{11}	11^{6}	5^{4}	Total	60^{27}	12^{11}	11^{6}	5^{4}

Superscripts represent numbers of bacteremic patients.
* Includes cases in whom empyema obscured the termination of the pneumonia.

hours after the first dose of drug, but a considerable number of patients first received serum on the third day of chemotherapy or later (table 5).

Duration of Acute Illness after the Beginning of Treatment (tables 4 and 5). Among the patients who recovered, 71 per cent of those treated with sulfapyridine alone and 63 per cent of those treated with sulfathiazole alone were afebrile and essentially symptom free within 36 hours after the first dose of the chemical. About one-half of those who received serum in addition and recovered were afebrile within the same interval after the drug was started. However, more than one-half of the latter had a crisis within 12 hours after the first dose of serum.

Untoward Reactions. The toxic effects of sulfapyridine and sulfathiazole in the cases of pneumococcic pneumonia are listed in table 6. With the former, the symptoms noted and their frequency were essentially similar to those observed in the previous year. In the sulfathiazole treated

cases nausea and/or vomiting was noted in 42 per cent of the cases, as compared with 54 per cent among sulfapyridine treated cases. Vomiting of moderate or severe degree was, however, uncommon with the former and quite frequent with the latter, in spite of the application of a large variety of measures aimed to prevent or alleviate this symptom. In five of the sulfapyridine treated cases the vomitus contained moderate to large amounts of blood. Four of these patients died; in two of them the source of bleeding was found in the small intestine and in a third it originated in esophageal varices.

TABLE VI

Numbers of Patients Showing Various Untoward Effects from Chemotherapy

Toxic Effect	Sulfapyridine (518 cases)	Sulfathiazole (169 cases)
Nausea and/or vomiting:	279	71
Nausea alone	30	13
Mild vomiting	94	38
Moderate vomiting	120	19
Severe vomiting	35	1
Hematemesis	5	0
Diarrhea	2	0
Hematuria:		
Gross	6	3
Microscopic	8	2
Crystals (acetylated drug?) in urine	18	20
Nitrogen retention in blood *	18	3
Anemia †	13	1
Leukopenia ‡	7	1
Drug rash	5§	5
Drug fever	13	8
Fever after drug stopped	14	6
Relapse of pulmonary infection ‖	22	3
Delirium or depression	11	2
Toxic hepatitis	0	1

* Increase of 20 mg. per cent or more of non-protein nitrogen during treatment.
† Drop of 20 per cent or more in hemoglobin during treatment.
‡ Drop in leukocyte count below 4000 per cu.mm. during treatment. One of sulfapyridine treated cases died of agranulocytosis.
§ Includes one with mucous membrane lesions.
‖ During treatment or within 10 days of the time the drug was discontinued.

Hematuria was about as frequent with the one drug as with the other. In most instances it was discovered only on microscopic examination of the urine. Nitrogen retention was more frequent in the sulfapyridine treated cases. Characteristic crystals presumably of the acetylated form of the drug, were seen on microscopic examination of the voided urine and were more frequent in the sulfathiazole treated cases. The crystals were often seen in the specimen bottles after the urine was allowed to stand for a while. Microscopically, the sulfapyridine crystals appeared in irregular clumps of blade-like crystals, while the sulfathiazole crystals were long and thin and the clumps assumed forms like sheaves of wheat.[3] Crystals were seen in almost all of the cases with hematuria.

Anemia and severe leukopenia were considerably more frequent in the sulfapyridine recipients. One of the latter died of agranulocytosis which developed on the sixteenth day of treatment. Leukopenia has been noted more frequently among patients treated with sulfathiazole for conditions other than pneumococcic pneumonia. One such patient died of agranulocytosis during the fourth week of treatment for subacute bacterial endocarditis.[11]

Drug fevers and drug rashes were more frequent with sulfathiazole. Three of the rashes observed were accompanied by typical lesions of erythema nodosum on the extensor surfaces of the arms and legs, particularly around the knees and elbows. Two of the latter had erysipeloid lesions of the face with edema of the eyelids, but the scleral and conjunctival lesions described by Haviland and Long [4] were not seen. Rashes and fevers were both seen with even greater frequency among cases treated with sulfathiazole for other diseases.

Relapses of fever and symptoms and reactivation of the pulmonary lesion were frequent. They usually occurred within 48 hours after the drug was discontinued—sometimes after an obviously inadequate total dose. In three of the cases these relapses were associated with a different type of pneumococcus; in three instances they were probably related to the acquisition of fastness by the original infecting pneumococcus [5]; in three others bacteremia with the same type recurred during or after two to six days of drug therapy; while in several patients no pneumococci could be found after thorough search of typical, freshly raised rusty sputum obtained at the time of the relapse. The response to further chemotherapy during the relapse varied; some patients had a typical and rapid drop in fever while others failed to respond at all or improved only after specific serum was given. In a number of other patients, fever recurred as soon as the drug was discontinued, although there was no evidence of focal complications or of a reactivation of the pulmonary lesion.

Untoward reactions from specific serums were few and mild. Thermal reactions (chills) occurred in 17 of the 92 serum recipients, including the four who had no chemotherapy. All the chills were mild and only three patients had chills after more than one injection. Immediate reaction in the form of dyspnea and nausea occurred after one of the injections in each of five patients, a typical asthmatic attack occurred in one case and urticaria in another. Serum sickness with arthralgia and/or urticaria was noted in six patients, while seven others had only a low grade fever about one week after the serum administration which may have been a manifestation of serum sickness.

Complications. Postpneumonic complications were of the usual variety and occurred in about the same frequency as in the previous year. Most of the patients in whom infected purulent fluid was obtained by thoracentesis and who recovered eventually required surgical drainage by rib section. In three patients the empyema cleared without such intervention; all of these

TABLE VII
Complications

Complication	Treated with Sulfapyridine				Treated with Sulfathiazole				No Specific Treatment		All Cases
	Alone		Plus Serum		Alone		Plus Serum				
	Recovered	Died	Recovered	Died	Recovered	Died	Recovered	Died	Recovered	Died	
Empyema*	6^{1}	6^{1}	4^{4}	3^{1}	1	1	3^{3}	1	2	4^{3}	31
Pericarditis	—	1	—	—	1	—	—	—	—	4^{3}	6
Endocarditis, vegetative	—	3^{3}	—	2^{2}	—	—	—	—	—	7^{6}	12
Meningitis	—	1	—	1	—	—	—	—	—	1^{1}	3
Peritonitis	—	1	—	—	—	—	—	—	—	1^{1}	2
Arthritis, suppurative	—	1	—	—	—	—	—	—	—	—	1
Lung abscess	—	1	—	—	—	—	—	—	—	—	1
Sterile effusion	11^{3}	1^{1}	7^{3}	—	9	1	—	—	1	1	31
Atelectasis	5^{1}	—	1	—	1	—	1^{1}	—	2	—	10
Otitis: catarrhal	3	—	—	—	1	—	—	—	—	—	4
suppurative	4	—	—	—	1	—	—	—	—	—	5
Subcutaneous abscesses	1^{1}	—	1	1^{1}	2^{1}	—	—	—	—	—	5
Streptococcus sepsis	—	2	—	—	1	1	—	—	—	3^{1}	7
Jaundice	2^{2}	1^{1}	3^{1}	1^{1}	1	—	—	1	—	1	10
Relapse after drug therapy	17^{6}	—	4^{2}	1^{1}	3	—	—	—			25
Extended during drug therapy	2	—	—	—	3^{1}	—	—	—			5

Superscripts represent number with positive blood cultures.

* Only 3 recovered without operative drainage (1 treated with sulfapyridine and 2 treated with sulfapyridine and serum). The empyema was of the "putrid" type with mixed bacteriology and probably associated with pulmonary abscess in 6 of the sulfapyridine treated patients (of whom 3 died), and in 1 of the untreated patients who recovered. The one who recovered after sulfapyridine treatment required no surgical intervention.

patients received sulfapyridine and two were given serum in addition. Only small amounts of fluid were obtained in these cases. Of interest is the fact that in seven of the empyemas, six of which occurred in sulfapyridine treated cases and one in a patient who received no specific treatment, the fluid was putrid or subsequently became putrid. These cases were probably associated with abscess formation in the lungs, but this was verified in only one patient who developed a broncho-pleural fistula. Four of these seven patients recovered, including the patient who received no specific treatment and the sulfapyridine treated patient who recovered without surgery.

Sulfathiazole in Non-Pneumococcic Pneumonias

In the period covered in this report, 95 additional patients with pneumonia were treated with sulfathiazole, but bacteriological studies of blood and sputum failed to reveal the presence of pneumococci. In some of these cases the predominant or only organisms cultured were hemolytic streptococci and *Staphylococcus aureus,* but in the majority the sputum yielded only ordinary mouth organisms, predominantly streptococci, which exhibited varying degrees of hemolysis. Among these patients the response to treatment varied much more than among the pneumococcic pneumonias, some showing rapid and dramatic critical recoveries while in others the disease was apparently refractory to the drug. Clinically, 24 were diagnosed lobar pneumonia and 71 atypical or bronchopneumonia. A large proportion of the latter were secondary pneumonias, but some were probably primary pneumococcic pneumonias in which the materials available for bacteriological study were inadequate or unsatisfactory. There were four deaths among the lobar pneumonias and 18 among the atypical pneumonias, giving a mortality of 23 per cent for the entire group. No accurate data are available for a satisfactory evaluation of the results in such cases, but many of them were undoubtedly helped by the drug and some lives were probably saved in this group. To be sure, in some of the cases included under the pneumococcic pneumonias, the relation of the pneumococcus to the disease is not always clear. This is particularly true among the cases with higher types, where the mortality was greater than among those with the more common types.

Discussion

The focus of attention in the treatment of pneumonia at the time of this writing is centered on the relative merit of sulfathiazole and sulfapyridine. From the point of view of the gross mortality, the data at first glance suggest a definite superiority of sulfathiazole. When corrected for the age distribution, however, the mortality with each drug was about the same. Others have found a slightly lower mortality with sulfathiazole in seemingly comparable cases,[6] but the data from most of the clinics in which this drug received extensive clinical trials are yet to appear and may shed more light

on this point. Laboratory data concerning the relative effectiveness of these drugs are somewhat conflicting.[7] Our own studies in vitro with freshly isolated strains[5] indicate that these two drugs have an almost identical effect in equal concentrations on most pneumococcus strains. When differences were noted, they were all slight but they indicated that for some strains sulfathiazole may produce the same effect as sulfapyridine with slightly smaller concentrations.

That the amount and severity of the nausea and vomiting are appreciably less with sulfathiazole is generally agreed, and this alone may be a determining factor in the success or failure of chemotherapy in certain cases. Inadequate dosage is used in some patients, while in others treatment is interrupted or discontinued too soon because of the vomiting. This alone may occasionally result in a fatality that might have been avoided. The frequency of relapses with sulfapyridine, on the one hand, and the greater average total dose of sulfathiazole, on the other, are, in a certain measure, reflections of this effect. Anemia and leukopenias were also less frequent in the sulfathiazole treated cases.

Certain other important untoward effects, notably drug rashes and hematuria, are more frequent and probably more severe with sulfathiazole than with sulfapyridine, as indicated in the present cases and in our general experience with these drugs to date. The renal complications are of particular interest, since the smaller degree of acetylation of sulfathiazole in both blood and urine is usually offered as one of the chief advantages of this drug over sulfapyridine. To be sure, the acetylated form of each of these drugs is inactive therapeutically and is quite insoluble and therefore undesirable. However, the decreased acetylation of sulfathiazole is associated with a much more rapid excretion of the drug into the urine, so that it is more difficult to maintain high levels in the blood while greater concentrations of the drug are excreted into the urine. The opportunities for the development of hematuria and other manifestations of severe renal damage may thus be as great as with sulfapyridine, if not actually greater.[3, 8]

On the whole, it may be concluded that (*1*) both sulfapyridine and sulfathiazole are about equally effective in the treatment of the pneumococcic pneumonias and (*2*) the administration of both of these drugs is accompanied by toxic symptoms which vary somewhat in frequency and severity. Since vomiting is less frequent and less severe with sulfathiazole, this drug is easier to give in adequate doses and is therefore to be preferred in most cases.

The relative merits of serotherapy and chemotherapy and the advantages of using serum early, in addition to drugs, in the severe cases of pneumococcic pneumonia have been discussed in the last year's reports.[1, 9] The experience of the present season has in no wise altered the conclusions reached at that time.

The gross mortality in all the cases that were treated specifically with chemicals and/or serums during the present year was about the same as in

the previous year. This fact is of interest since a number of American authors who reported unusually low mortality rates during their first year's experience with sulfapyridine were inclined to attribute their favorable results in part to the mild character of the pneumonia during that season. Higher mortalities during the present season, such as were reported by the Philadelphia workers,[6a, 10] would tend to bear out such an assumption. Our experience, however, has led us to feel that the differences in severity of pneumonia from year to year, at least when one is dealing with the same type of clinical material, are explicable on the basis of the relative frequency of the important prognostic factors such as those analyzed in this and in similar reports.

Summary and Conclusions

The essential data concerning the 911 cases of pneumococcic pneumonia treated at the Boston City Hospital between July, 1939 and June, 1940 have been presented and analyzed.

Specific therapy, consisting essentially of sulfapyridine or sulfathiazole, supplemented in some of the cases by type-specific antipneumococcic serums, was used in 76 per cent of the cases, and the gross mortality in these cases was 16.4 per cent.

Sulfapyridine and sulfathiazole were used in the same manner. The results of treatment with these two drugs were essentially the same when due allowance was made for the difference in incidence of patients over 60 years of age.

The administration of both sulfapyridine and sulfathiazole is accompanied by untoward effects which vary somewhat in frequency and severity. Anemia, leukopenia and relapses were more frequent among the sulfapyridine treated cases. Drug rashes were more frequent among the sulfathiazole recipients, while hematuria was about as frequent with the one drug as with the other. The most common toxic effect of both drugs, however, was the nausea and vomiting, and this symptom was considerably less frequent and less severe among the cases treated with sulfathiazole, making this drug considerably easier to give to the large majority of patients.

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LIVER FUNCTION IN HYPERTHYROIDISM, WITH SPECIAL REFERENCE TO THE GALACTOSE TOLERANCE TEST *

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Review of Literature

The endocrines may influence the functions of the liver, mainly the glycogenic function.[1, 2, 3] Claude Bernard regarded glycogen as an internal secretion product of the liver and recognized connections between this substance and other endocrine products.

Experimental data, pathological observations, clinical jaundice in patients with exophthalmic goiter, and liver function studies establish the fact that the liver is frequently damaged in hyperthyroidism.

The evidence in the literature upon which the connection between hyperthyroidism and liver damage has been established will be presented as follows:

(1) experimental; (2) anatomic changes in the liver; (3) clinical cases of jaundice; (4) liver function tests in patients with exophthalmic goiter.

1. Experimental: A large proportion of the investigations in this field deals with carbohydrate metabolism. The glycogen content and pathological changes in the liver after feeding small and toxic doses of thyroid, and the influence of the liver on the thyroxine molecule and of thyroxine on the composition of bile have been studied.

Experimental hyperthyroidism has been produced in animals (cats, guinea pigs, dormice) by excessive feeding of thyroid substance (Farrant, 1913).[4] The studies of Cramer and Krause (1913)[5] demonstrated that the addition of thyroid to the diet of cats and rats resulted in almost total disappearance of glycogen from the liver. Parhon (1913)[6] and Kuriyama (1917–1918)[7] confirmed this observation also in rabbits. The former attributed the glycogen depletion in the liver to an inhibition of glycogenic function, the latter to an increased glycogenolysis in the liver. Similar confirmatory studies have been reported by Abelin and Jaffe (1920),[8] Romeis (1923),[9] Fukui (1925),[10] Boesl (1928),[11] Abderhalden and Wertheimer (1928),[12] Abelin and Spichtin (1930),[13] Lawrence and McCance (1931),[14] Knittel (1931),[15] Althausen and Thoenes (1932),[16] Coggeshall and Greene (1933),[17] and Frazier and Frieman (1935).[18] Fukui (1925) found liver glycogen depletion in rats so uniform that he suggested it as

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a method of assay for thyroid preparations. Frazier and Frieman (1935), however, could not confirm the direct relationship between thyroid dosage and glycogen depletion. Himmelberger (1932) [19] reported the disappearance of liver glycogen in mice after the injection of blood or urine from hyperthyroid subjects. Eitel, Loehr and Loeser (1933–34) [20] injected guinea pigs with the thyrotropic substance from the anterior lobe of the pituitary and found a decrease in liver glycogen. Removal of the thyroid gland prevented this effect. Kuriyama (1918), Frazier and Frieman (1935), and Loeser (1934) found that the glycogen depletion could not be prevented by the feeding of large amounts of carbohydrate. Wilder and Sansum (1926) [21] concluded from studies of the respiratory quotient that the carbohydrate is adequately utilized, the decreased glycogen being probably due to faulty storage of carbohydrate in hyperthyroidism.

The influence of thyroxine on tissue oxidation has been measured. Reinwein and Singer (1928) [22] demonstrated an increased use of oxygen by living liver cells when this substance was applied to them in certain concentrations; an inhibiting effect was noted in higher concentrations. According to Dresel, Goldner, and Himmelweit (1929) [23] thyroxine has only a slight direct effect if any at all on tissue oxidation. After the injection of thyroxine, split products derived from proteins appear in the liver in increased amounts. It is these, and especially tyrosin, which they held responsible for the elevated rate of oxidation. The thyroxine leads to increased output of tyrosin, and tyrosin, in turn, combining with iodine in the thyroid, builds thyroxine. In 1925, Schryver [24] found that the livers of thyroid-fed animals showed a greater degree of autolysis after 24 hours than those of non-thyroid-fed control animals. However, when thyroid was fed for eight days or more an opposite effect was noted.

The prolonged feeding of thyroid produces other changes in the liver which more than offset the loss of weight due to lack of glycogen or the possible increase of cellular activity. Higgins (1933) [25] found that the livers of rats fed a thyroid ration increased in size and also in the extent of the restoration of the liver following partial surgical removal. Simonds and Brandeis (1930) [26] had noted a similar relative increase in the weight of the liver in thyrotoxic dogs. Hoskins (1916) [27] and Hewitt (1919–1920) [28] earlier observed relatively heavier livers in thyroid-fed rats.

The rôle of the liver in thyroxine metabolism has been investigated. Zavadovsky and Perelmutter (1927) [29] found that the liver of fowls played an important rôle in decomposition and excretion of thyroxine. Blum and Grutzner (1920) [30] demonstrated in dogs the power of the liver to decompose thyroxine and split up iodine-containing fractions into more elementary forms. Kendall (1919) [31] administered 200 mg. of thyroxine to dogs and in less than 20 hours 43 per cent of the iodine elements of the thyroxine had been excreted in the bile. Krayer (1928),[32] working with rats, obtained results similar to those of Kendall.

Thyroxine administration may alter the composition of liver bile. Leites

and Isabolinskaja (1933) [33] found an increase in cholesterol concentration in the bile and in most cases an absolute increase of the amount of cholesterol excreted in a 24 hour collection. The total bile acids and the amount of biliary secretion were also increased. The calcium and potassium content remained unchanged. Besuglow and Tutkewitsch (1933),[34] using the same experimental method, reported a fall in cholesterol concentration of bile after the injection of 2 mg. of thyroxine and a rise after total thyroidectomy. Parhon and Werner (1931) [35] reported findings similar to those of the latter workers. Johnson and Riegel (1939) [36] were unable to demonstrate any effect on the cholesterol concentration or total cholesterol output of the hepatic bile in thyroid-fed or thyroxine-injected dogs despite the fact that the blood cholesterol fell considerably. Following total thyroidectomy the bile cholesterol remained unchanged, although the blood cholesterol rose considerably.

Experimental hyperthyroidism may result in hepatic changes. Farrant (1913) noticed fatty degeneration at the center of the lobules in rabbits. Hashimoto (1921) [37] found parenchymatous degeneration of the liver cells about the efferent veins varying from fatty degeneration to necrosis. These changes were sometimes found throughout the lobule, but were never confined to the periphery. Hypertrophy of liver cells, mitotic figures and double nuclei were found in the peripheral zones. While the evidence of chronic passive congestion coincided with marked myocardial changes, the parenchymatous degeneration did not. Gerlei (1933) [38] obtained centrilobular necrosis in rabbits after five to seven days with fatal doses of thyroxine subcutaneously.

The possibility that excessive thyroid feeding may potentiate the action of toxic agents was not supported by observations of Davis and Whipple (1919) [39] which indicated that thyroid feeding of dogs did not aggravate the liver injury following chloroform anesthesia. Cameron and Karunaratne (1935) [40] tested the above hypothesis by feeding albino rats large doses of thyroid extract and then determining their minimal toxic dose for carbon tetrachloride. No alteration was found from the dose previously estimated for normal control animals from the same litters.

2. *Anatomical Changes in Hyperthyroidism:* The anatomical changes in the liver in exophthalmic goiter have been reviewed by Weller (1932–1933),[41] Haban (1933–1934),[42] Beaver and Pemberton (1933),[43] Rössle (1933),[44] and Cameron and Karunaratne (1935). Distinction has been drawn between two main groups of anatomical changes in the liver depending on whether or not passive venous congestion is deemed responsible for pathological changes. The changes noted in the non-congestive cases have been interpreted as representing reactions to varying degrees of injury, the result of thyroid derangement. The pathological changes resolve themselves into three main types: (1) Acute degenerative hepatic lesions in the form of marked fatty change and actual necrosis of either focal or central type, the latter appearing to represent an accentuation of the same toxic

reactions which usually resulted in the fatty change. The fatty degeneration appears to progress sometimes to necrosis and sometimes to chronic changes such as: (2) Atrophy, local or general, or (3) Cirrhosis. Combinations of all forms exist. In rare instances acute liver atrophy has been reported. To these Rössle (1933) added the changes of "serous hepatitis" with capillary alterations. This type of change was not found in cases examined by Zeldenrust and Van Beek.[45] Thus the pathological changes may be grouped under seven headings: passive congestion, fatty changes, atrophy, cirrhosis, cellular infiltration, necrosis and regeneration.

The complete absence of glycogen in livers of patients who died of exophthalmic goiter has been reported by Pettavel (1914) [46] and Wegelin (1926).[47]

The co-existence of cirrhosis of the liver and thyroid disease was first referred to by Paul (1865),[48] and by Trousseau (1868).[49] Subsequently, Farner (1896),[50] Askanazy (1898),[51] Dinkler (1900),[52] Marine and Lenhart (1911),[53] Landau (1911),[54] Pettavel (1912),[55] Rautmann (1915),[56] and Holst (1923) [57] referred to cases of cirrhosis as a complication of exophthalmic goiter. Descriptions of the cirrhotic changes have been given by Marine and Lenhart (1911), Haban (1933–1934), Weller (1933), Rössle (1933), Beaver and Pemberton (1933), and Cameron and Karunaratne (1935). Although similar changes may occur in various chronic diseases in the same age groups, Weller and Haban intimate that the increased incidence and degree of portal changes and fibrosis in the subjects with thyroid disease suggest the existence of a distinctive type of thyroid cirrhosis, e.g., cirrhosis basedowiana (Haban). The chronic changes in the liver result in general atrophy with a decrease in size and weight of this organ. In these cirrhotic livers a characteristic is the presence in certain areas of dilatation of the portal canals with surrounding lymphocytic infiltration, without general alteration in lobular structure. More advanced stages of this lesion occur in which the widened portal canals become united by narrow bands of connective tissue. There may be considerable alteration in the lobular structure, and also annular fibrosis encircling hepatic lobules. "Nodule" formation may be found mainly along the surface or along the edge of the liver, and occasional nodules occur in the deeper portions of the organ. These nodules are well outlined by fibrous tissue bands and bordered by grooves of depressions. Microscopically there is evidence of regeneration in both the liver cells and ducts.*

Significant decrease in the size and the weight of the liver has been reported by Beaver and Pemberton and by Cameron and Karunaratne. Bar-

* The incidence of chronic changes in the livers of patients who have died of Graves' disease varies in published reports. Weller [41] found what he called patchy chronic parenchymatous interlobular hepatitis in 65 per cent of his cases of exophthalmic goiter and in only 2 per cent of a controlled series. The liver changes were irregularly distributed; many lobules appeared normal. Beaver and Pemberton [43] observed what they termed subacute toxic atrophy and toxic cirrhosis in 60 per cent of the cases. Cameron and Karunaratne [40] found cirrhosis in the insular, interinsular or annular stages in 10 of their series of 30 cases (33 per cent).

tels (1938) [58] compiled and compared the published weights of normal livers and of the hyperthyroid series of Rössle, Cameron and Karunaratne and Beaver and Pemberton and found that the weight of 50 normal livers (Boyd 1933) [59] averaged 1424 grams compared with the average weight of 1232 grams for 167 hyperthyroid livers. This is contrary to the experimental observations of Simonds and Brandeis (1930) on dogs rendered thyrotoxic by feeding desiccated thyroid. In these animals, even though the loss of body weight was severe the liver lost relatively little weight. Apparently the results of the experimental observations cannot be transferred to cases of exophthalmic goiter. There does, however, appear to be a direct relationship between the loss of body and liver weights, the extent of the pathological process, and the clinical severity of the disease in a correlation of clinical and postmortem data (Beaver and Pemberton). There also appears to be a correlation between the pathological findings in the liver and the duration of the clinical history, on the whole. Cameron and Karunaratne found that the cases of more advanced cirrhotic changes gave a longer history (one to three years at least) and those with less advanced lesions, i.e., insular or interinsular fibrosis (four months to two years).

3. Clinical Jaundice: The jaundice which occurs in the course of exophthalmic goiter has, in rare instances appeared to be explainable by the associated congestive heart failure. In the majority of cases, however, the thyrotoxic disease itself appears to be the direct cause of the jaundice. In occasional instances the jaundice is due to associated intercurrent disease of the liver and bile passages.

The occurrence of jaundice has been mentioned in the communications of Habershon (1875),[60] Eger (1880),[61] Gaill (1883),[62] Strümpell (1886),[63] Burton (1888),[64] Westedt (1889),[65] Boinet and Bourdillon (1891),[66] Moebius (1896),[67] Sutcliff (1898),[68] Dieulafoy (1901),[69] Sattler (1906),[70] Rautmann (1914–1915),[56] Chvostek (1917),[71] Marine and Lenhart, Crotti (1922),[72] Boothby (1922),[73] Klose (1929),[74] Barker (1930),[75] Assmann (1931),[76] Heilmeyer (1931),[77] Lichtman (1932),[78] Beaver and Pemberton (1933), Retzlaff (1937).[79]

In every instance of jaundice complicating hyperthyroidism an unrelated cause for jaundice must be ruled out. Assmann (1931) emphasized this fact and Lichtman (1932) referred to two cases of terminal jaundice complicating thyrocardiac disease in which the jaundice was accounted for by cholangitis histologically. Clinically it had appeared that the jaundice was directly connected with the thyrocardiac disease. Assmann emphasized the possible association of hyperthyroidism with cholelithiasis, syphilis, and other common causes for jaundice. Eder (1906) [80] maintained that the jaundice arose from some chronic intestinal toxemia, and that possibly the same intoxication precipitated the hyperthyroidism. Boothby (1922) noted that clinical jaundice was not uncommon in the late stage of long continued gastrointestinal crises in cases of Graves' disease. Crotti (1922) also re-

ferred to the yellow tint of the sclerotics which may occasionally be observed in thyrotoxic patients during severe gastrointestinal disturbances.

Outspoken jaundice of the skin and sclerae is rare in exophthalmic goiter. The observation of Beaver and Pemberton would indicate that jaundice occurred in approximately 20 per cent of 107 cases. However, in approximately 75 per cent of their cases the jaundice was extremely mild (Grade 1), and in only one instance was it severe. The general impression exists that jaundice occurs only in the severe thyrotoxic cases. Approximately one-third of cases with jaundice in Beaver and Pemberton's series were in or on the verge of thyroid crises before death.

In the course of a decade, Dr. Paul Klemperer, Pathologist to the Mount Sinai Hospital, has made anatomical examinations in 26 cases of Graves' disease. Jaundice occurred in only two instances (8 per cent). The ages of these patients were 30 and 34 years respectively and they had suffered from Graves' disease over a period of seven and two years respectively. There was no heart failure in either case and the jaundice was attributed directly to Graves' disease.

4. Liver Function in Hyperthyroidism: The appearance of jaundice in the course of thyrotoxicosis and a search for the cause of the thyroid crisis have led to repeated studies of the functional activity of the liver in clinical hyperthyroidism. Bauer, when he introduced the galactose tolerance test, noted a disturbance in the tolerance for this sugar in Graves' disease. Hirose (1912) [81] found that patients with hyperthyroidism had an alimentary galactosuria similar to that found in cirrhosis and catarrhal jaundice. This was confirmed by Strauss (1913, 1930).[82] Sanger and Hun (1922) [83] found abnormal glucose tolerance curves in hyperthyroidism which they attributed to a failure of the liver to store glucose, due to some toxic change in the liver. Youmans and Warfield (1926) found a moderate degree of disturbance in dextrose and levulose tolerance. They concluded that there appeared to be no proportionality between the degree of impairment of liver function and the increase of the metabolic rate. There was some correlation between the loss of weight and the disturbance of liver function in 10 cases of exophthalmic goiter. Kugelmann (1930) [84] obtained evidence of a disturbance of hepatic function by means of the levulose tolerance test. Adler and Lemmel (1928) [85] noted abnormal ester cholesterol partition in a few cases of severe exophthalmic goiter. The ester fraction was decreased as in cases of liver damage. They attributed fatty stools sometimes observed in this disease to disturbed fat metabolism.

The change in carbohydrate metabolism in exophthalmic goiter, as evidenced by a depletion of glycogen in the liver, was made the basis of a biological test for thyroxine by Dresel and Goldner (1929) [86]; and Willis and Mora (1931) [87] applied this principle as a biological test for hyperthyroidism using the liver of the mouse as a test object. Himmelberger (1932) adapted the technic of the mouse test for urine as well as blood serum of patients with Graves' disease.

Some evidence of bile pigment metabolism disturbances in hyperthyroidism has been reported. Youmans and Warfield (1926) studied the liver function in 44 cases of thyrotoxicosis, including cases with passive congestion of the liver by means of the phenoltetrachlorphthalein test. They found retention of 3 to 10 per cent of this dye in the blood after 60 minutes in 22 of 48 cases (45 per cent) and elevated icterus index in seven of nine cases. Seven patients in the series were clinically jaundiced. Passive congestion and pneumonia may have contributed to the pigment metabolism disturbance independently of thyroid disease. These authors could detect no hepatic functional impairment, as measured by the dye excretion test in dogs that had been fed a large amount of thyroid extract. Heilmeyer (1931) found the urobilin quotient (urine/stool urobilin) to be elevated in three of six cases investigated. As tested by the method of Bergmann and Eilbott (1927) [88] the bilirubin excretion power of the liver was found to be impaired in five cases. Toxic injury of the liver due to thyroid hormone rather than circulatory failure was considered to be responsible.

Maddock, Coller and Pedersen (1936) [89] studied the liver function by means of the bromsulphalein dye test and serum bilirubin. Of 13 patients with toxic goiter 8 or 61 per cent showed evidence of liver damage before operation as measured by an increase in serum bilirubin above 3 mg. per liter and above 10 per cent bromsulphalein dye retention. There appeared to be some correlation between the severity of the hyperthyroidism, as measured by basal metabolic rate, and the functional impairment. In five hyperthyroid patients with normal function tests the basal rate averaged 33 per cent as compared with an average of 54 per cent for eight patients with abnormal liver function tests. A relation was found to exist between the severity of the disease and the degree of liver damage. There was no correlation between the level of preoperative liver function impairment and the incidence of postoperative reactions. In the postoperative period an increase in the incidence and degree of impaired hepatic function and an increase in hyperthyroid reactions were found but there was no evidence to show that one was the cause of the other. Furthermore, direct relationship between impaired liver function and thyroid crisis has been disclaimed by Foss, Hunt and McMillan (1939).[90] Lichtman [78] found no significant increase in the icterus index in thyrotoxic cases without heart failure.

Bartels [58] observed reduced liver function by means of the hippuric acid excretion test in a high proportion of cases of hyperthyroidism (87 per cent). No apparent correlation was found to exist between the liver function and the duration of hyperthyroidism. The degree of change in liver function was found to be directly related to the severity of hyperthyroidism as measured by the basal metabolic rate and the degree of weight loss. Three months after thyroidectomy normal liver function was restored in a high per cent of cases indicating that the liver damage is rarely permanent. A high carbohydrate diet apparently improved the liver function as measured by this test.

Ragins (1936) [91] applied the Takata-Ara reaction to cases of exophthalmic goiter and found positive reactions in six cases. A negative reaction was obtained in seven cases of exophthalmic goiter and one in toxic adenoma. Madden, Winslow, Howland and Whipple (1937),[92] studying blood plasma protein in regeneration found that powdered thyroid fed in doses sufficient to accelerate body metabolism showed no distinct effect on plasma protein production which was not attributable to the protein in the thyroid powder itself.

Althausen and Thoenes (1932) [93] applied a modification of the dextrose tolerance test followed by an injection of epinephrine. Typical hypoglycemia was not produced. In patients with liver disease characterized by lowered glycogen content of the liver, this modified dextrose tolerance test is followed by hypoglycemia. The impaired function of the liver would appear then to be dependent on factors other than depletion of liver glycogen. Althausen and Wever (1937) [94] endeavored to obtain further information as to the cause of decreased sugar tolerance in hyperthyroidism by studying the response of patients with this disease to galactose.* The curve of galactose in the blood after oral administration with sugar was higher in patients with hyperthyroidism than in normal or diabetic subjects. The changes in galactose tolerance were not proportionate to the severity of hyperthyroidism judging by any one criterion. This was deemed not remarkable considering that the basal metabolic rate and other manifestations of hyperthyroidism do not necessarily correspond in severity. Thyroidectomy in most instances restored normal tolerance to galactose. The estimation of amino-acid nitrogen in the blood proved to be normal.

Lichtman (1932) [78] found a disturbance of cinchophen oxidation in 16 of 20 (80 per cent) cases of uncomplicated hyperthyroidism. The capacity of the liver cells to oxidize this substance was moderately impaired. Larger than normal amounts of oxy-cinchophen, a partial oxidation product of cinchophen, appeared in the urine after a test dose. With this test there was in no instance evidence of severe impairment and no direct relationship was noted between the degree of liver damage and level of metabolic rate, duration of the disease, or degree of weight loss.

Personal Observations

In the course of the development of a modification of the technic for the performance of the galactose tolerance test based on a differentiation of galactose and glucose in urine by means of yeast fermentation after the oral

* The value of the galactose test as a study of liver function in patients with hyperthyroidism is not, in our opinion, depreciated by Althausen's observation [95] that there is an increased rate of absorption of galactose from the intestinal tract in this disease. This may be due to the associated increased rate of blood flow through the tissues in this disease. There is also, however, a coincident increased rate of oxidation of carbohydrate in the tissues. On the basis of an increased rate of absorption alone, it is, therefore, erroneous to conclude that the status of galactose tolerance as a liver function test is necessarily altered in hyperthyroidism. Furthermore, the fact that 54 per cent of the galactose tolerance tests in our series of cases of hyperthyroidism gave normal results suggests that increased intestinal absorption of galactose is not the underlying factor in the pathological galactosurias.

ingestion of the standard dose of galactose,[96] observations were made on the galactose tolerance in 13 patients with thyrotoxicosis.* The results indicated a normal galactose excretion varying between 1.1 and 2.4 grams in seven of 13 cases (54 per cent) (table 1). In the remaining six cases

TABLE I

Thyrotoxicosis and Normal Galactose Tolerance

Case No.	Age	Sex	Weight Loss Lbs.	Duration of Disease Months	B.M.R. Per Cent	Galactosuria,* Grams
1. S. S.	14	F	15	2	+24–12†	1.2 (Lugolization before Admission-Remission Stage)
2. L. S.	19	F	0	2nd stage	+26–9	1.4 (1st stage Thyroidectomy 6 months previously)
3. S. A.	33	F	30	6	+33–23	1.6
4. C. B.	40	F	10	5	+84–25	1.4
5. A. K.	41	F	24	3.5	+29–26	2.2
6. M. K.	50	M	5	3	+35–22	1.1
7. I. D.	55	F	50	12	+52–52	2.4 2.4 (Congestive Heart Failure)
Average	33		19	5.3	+40–25	

* Galactose tolerance performed before or promptly after the beginning of lugolization.
† Initial B.M.R. and lowest B.M.R. after lugolization or thyroidectomy.

pathological galactosurias ranging between 3 and 12.5 grams were encountered. In six cases (8, 9, 10, 11, 12, 13—tables 2 and 3) the influence of iodine and thyroidectomy was noted. The data are too meager to permit any conclusion, except that there is a definite tendency for the galactose tolerance test to improve with the iodine therapy and consequent decrease of the basal metabolic rate. Cases 8, 9 and 11 illustrate the definite beneficial effect of thyroidectomy, i.e., the return to normal galactose tolerance. In case 10 there was a postoperative increase in the galactosuria and basal rate. The clinical results in this case also indicated that thyroidectomy was fol-

* In the author's new technic[96] for the estimation of galactose tolerance the sugar content of each fraction is determined before and after fermentation. The non-fermentable fraction is galactose. A correction is made for the galactose which may have disappeared from the mixture as determined in a galactose control. The fermented fraction then represents the glucose concentration present with the galactose. When fermentation is permitted to continue over a period of 24 hours, amounts varying between 0.1 and 0.7 per cent (0.3 per cent in the majority) of reducing substance was found to disappear in the process of fermentation. If a galactose solution is treated with a yeast suspension for one hour, at temperatures varying between 40 to 45° C., amounts up to 0.13 per cent may disappear. After 24 hours, as much as 0.38 per cent may disappear. In the author's technic, therefore, fermentation is carried on for one hour at the above temperature and the correction for disappearance of galactose by diffusion into the yeast cells is made from a galactose control.

lowed by a hyperthyroid reaction. Case 12 demonstrated return to normal galactose tolerance with lugolization. Cases 9 and 10 (table 2) confirm an observation made by Bartels, with the hippuric acid test, that normal function may not return after thyroidectomy for varying periods of time. In case 9 the liver function was still impaired on the fourth day after operation. By the tenth day it had returned to normal. In case 10 a determination made on the fourth day was abnormally high. In case 11, normal function had already returned on the fourth day postoperative.

TABLE II

The Influence of Iodine Therapy and Thyroidectomy on Pathological Galactosuria

Case No.	Age	Sex	Weight Loss Lbs.	Duration of Disease Months	B.M.R. Per Cent	Grams Galactosuria	
						Pre-operative	Post-operative
8. J. S.	42	F	15	6	+34–18*	5.4	0.68
9. R. F.	38	F	50	12	+79–36	3.0 4.2	3.48 (4th day) 2.0 (10th day)
10. S. H.	50	M	45	9	+48–20	6.8† 5.2 3.8	5.9 (4th day)
11. E. L.	42	F	10	5	+63–20	4.7 6.1‡ 3.9	2.2 (4th day)
12. E. H.	41	F	15	36	+37–17	4.0 1.2	
Average	43		25	14	+52–22		

* Maximum B.M.R. before and minimum B.M.R. after iodine (Lugol's sol.).
† Galactose tolerance tests performed at intervals during iodine treatment.
‡ At height of upper respiratory infection.

In the group of cases with normal galactose tolerance, the average age of the subjects was approximately a decade lower than that of the group with pathological galactosuria; the weight loss in the former group averaged six pounds less. The duration of the disease was nine months less in this group. The initial basal metabolic rate was, on the average, 12 per cent greater in the cases with abnormal galactose tolerance. It is significant that case 1 of the normal group had been treated with iodine before admission to the hospital and was in a remission stage, and that case 2 of this group had previously undergone a first stage thyroidectomy. The results of the galactose test appeared to correlate more uniformly than any other test with the clinical criteria of severity of the disease such as increased weight loss, duration of disease, and basal rate.

Of importance are the observations of the effect of infections on the galactose tolerance in the course of thyrotoxic disease (cases 11, 13—table

3). In case 11 a simple afebrile upper respiratory infection was accompanied by a rise in galactose excretion from 4.7 to 6.1 grams in spite of the fact that Lugol's solution was being administered. A corresponding rise in the basal metabolic rate also occurred. In case 13, during the development of a furuncle in the external auditory canal without fever, the excretion of galactose rose from 2 grams to 12.5 grams during the infection and then fell to 3.8 grams after subsidence of the infection. During the afebrile infection the basal metabolic rate rose from 33 to 41 per cent and subsequently dropped to 14 per cent.

TABLE III

The Effect of Infection on Galactosuria in Hyperthyroidism

Case No.	Basal Metabolic Rate			Galactosuria, Grams		
	Before	Infection	After	Before	Infection	After
11. E. L.	+20	42*	43	4.7	6.1	3.9
13. E. S.	+33	41†	14	2	12.7	3.8

* Upper respiratory infection. No fever.
† Furuncle of external auditory canal. Afebrile.

The special technic of performing the galactose test proved that the sugar excreted in the urine was essentially galactose. Carefully controlled yeast fermentation of a standard galactose solution, simultaneously with the test urines, disclosed the disappearance of small amounts of this sugar by means of adsorption and diffusion into the yeast cells. Yeast fermentation of test fractions without a galactose control might lead to the erroneous impression that the sugar which disappeared during the fermentation process was necessarily glucose.

COMMENT

There can be no question that the liver is frequently damaged in thyrotoxicosis. The accumulated data indicate that pathological changes may occur in the liver independent of those of chronic passive congestion due to heart failure. These changes may vary from simple acute fatty degenerative and necrotic lesions to a chronic form of atrophy and cirrhosis. On a pathological basis alone, one would expect abnormal results with the clinical liver function tests. In some cases certain tests may indicate no functional impairment and there may be only slight impairment even with the sensitive cinchophen oxidation and hippuric acid synthesis tests. In other cases all the tests indicate a slight to moderate functional impairment. Severe functional impairment is the exception, yet from the pathological lesions in severe cases of hyperthyroidism one would expect drastic functional changes. Discrepancies between the pathological lesions in the liver and the results of liver function tests occur as they do also in patients with heart failure. In heart failure, the cases exhibiting jaundice do not necessarily show the most

severe hepatic lesions (Kugel and Lichtman).[97] In some cases of Graves' disease jaundice may occur independently of the functional disturbances and is dependent upon a superimposed cholangitis or hepatitis (catarrhal jaundice). The instances of true acute yellow atrophy directly attributable to the thyrotoxic state are extremely rare. Considering the relative frequency of hyperthyroidism in the medical wards of a general hospital the incidence of jaundice in these cases is relatively uncommon. It occurred only in 8 per cent of our fatal cases.

The basic functional disturbance in the liver appears to be associated with carbohydrate metabolism. The data, however, indicate that it is not the glycogen depletion in the liver alone which is responsible for the abnormal liver function tests. There are actual anatomical changes in the liver cells. Toxic necrosis has also been described in the heart muscle and other tissues in this disease. Liver function tends to improve promptly with the administration of Lugol's solution, intravenous glucose therapy, and partial or total removal of the thyroid gland. Although the changes in the liver in some cases progress to chronic fibrotic disease, liver function appears to improve promptly after alleviation of the thyrotoxicosis by iodine administration or thyroidectomy.

The exact mechanism of the functional derangement of the liver is not established, but the following hypothesis may be advanced. The glycogen depletion in the liver is a physiological manifestation of the metabolic demands of the hyperthyroid state. The carbohydrate stores are exhausted and the protein stores also drawn upon for their carbohydrate fraction. This in itself should not produce liver function disturbance. However, glycogen exhaustion and protein depletion deprive the liver of its prime protective agents against poisons. The unprotected liver cell then may become vulnerable to thyroxine, products of endogenous intermediary metabolism or bacterial toxins from the intestinal tract or other foci in the body. The anatomical changes in the liver are produced by the action of these toxic elements.

The author's modification of the technic of estimating galactose in the test urines yielded the fact that sugar excreted in the urine during the test in this endocrine disorder is mainly galactose. The galactose test thus may be applied to the study of liver functions in endocrine disorders provided the excreted sugar in each instance is checked by yeast fermentation.

It is a common clinical observation that patients with hyperthyroidism tolerate upper respiratory and other infections poorly. The galactose test indicates that these infections further compromise the function of the liver even in the absence of fever. The damaging effect of infection on liver function has been reported elsewhere in other diseases such as tuberculosis (Steidl and Heise, 1935).[98]

Summary

A review of the facts reported in the literature and personal studies of liver function in patients with hyperthyroidism indicate that the liver is

frequently damaged, functionally and anatomically, in this disease. The anatomical changes are sometimes severe enough to produce functional changes. The changes may be regarded as representing varying degrees of reaction of this organ to the thyroid derangement. The following facts appear to have been established:

1. Employing various clinical liver function tests, 45 to 90 per cent of all cases of hyperthyroidism show some functional impairment, usually of slight to moderate degree. The cinchophen oxidation, the hippuric acid synthesis, and the galactose tolerance tests constitute the best measures for evaluating liver function in this disease. The galactose tolerance test appears to give results which may be more uniformly correlated with clinical criteria of severity of thyrotoxicosis, such as weight loss, duration of the disease, and basal metabolic rate. Other tests show either no correlation or only partial correlation with these criteria.

2. Factors which may directly improve impaired liver function are the administration of iodine and partial or total thyroidectomy. Normal function may be restored.

3. Upper respiratory infections (coryza) and other infections may aggravate existent liver function disturbance even in the absence of fever.

4. The sugar which appears in the urine following oral administration of galactose is mainly galactose.

5. The occurrence of jaundice in patients with thyrotoxicosis may be completely unrelated to the underlying hyperthyroid state and depend on intercurrent cholangitis, catarrhal jaundice or gall stones.

6. When jaundice is definitely determined by the thyrotoxicosis, it usually occurs in the severe cases.

7. There appears to be an increased degree of impaired liver function in thyroid crisis but there is no evidence to indicate that impaired liver function is the prime inciting agent in thyroid crisis.

A mechanism for the hepatic functional derangement in hyperthyroidism is suggested: The depletion of glycogen in the liver in this disease deprives the liver of its prime protective factor against poisons and establishes conditions conducive to damage by toxic agents, such as thyroxine, endogenous metabolic products, or bacterial toxins derived from the bowel or foci elsewhere in the body.

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LARGE HEALED TUBERCULOUS FOCUS (PROBABLY PRIMARY) SIMULATING METASTATIC CARCINOMA OF THE LUNG*

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KNOWLEDGE of the primary tuberculous complex dates from the work of Kuss (1898), Albrecht (1909), and Ghon (1912).† The pulmonary component of the complex, which is a zone of caseous pneumonia surrounding the site of the initial infection, is known in modern medicine as the primary or Ghon focus (tubercle). It is usually located subpleurally and is often very small, generally not larger than a bean, rarely larger than a hazel-nut. Over 95 per cent of cases have only one focus, and cases having more than two are very rare. It is most often found in the lower portion of the upper lobe or the upper portion of the lower. The right lung is somewhat more frequently involved than the left, and the upper lobes more often than the lower.[3, 9]

Roentgenographically, the focus is described by Köhler[6] as ranging in size from that of a hempseed to that of a pea, never seen in the apices, hilar region, or the middle of the lungs, but almost invariably in the lateral part of the lungs, not far removed from the lateral wall of the thorax; it is encountered at a level of from the second to the sixth intercostal spaces. Bigler[1] states that the ordinary primary lesion may not show on the roentgen fi'm unless it is 1 to 1.5 cm. in diameter, is near the lateral wall of the chest and not behind the diaphragmatic shadow, is surrounded by a definite area of atelectasis, or contains calcium.

Wallgren[11] has recently made an important contribution by following cases of childhood tuberculosis for a considerable number of years. Most primary lesions heal by fibrosis without calcification and the resulting scar is rarely visible roentgenographically. In the remaining cases, healing is by fibrosis with calcification. At least several years are required before calcification progresses to the point of radio-opacity. Wallgren has observed cases where the resulting calcified focus grew smaller and denser over a period of years due to the contraction of connective tissue and compaction of the lime. Then, in some, the lime began to absorb; decreased density thus resulted. Myers[8] and his co-workers have carried out similar studies. Initial lesions were observed to last from several months to a year or more, then to disappear, and subsequently become replaced by calcified shadows. In a series of 34 cases with enlarged hilar nodes, no visible parenchymal lesion, and a positive tuberculin reaction, 12 developed calcified Ghon foci after a lapse of several years.

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† Fried[2] has recently written a historical review on the primary tuberculous complex.

When seen in children these lesions usually present no serious diagnostic difficulties. During adult life, however, the failure to interpret properly such shadows may lead to errors in diagnosis. The following is a report of four cases in all of which, because of peculiar circumstances in their clinical course, large dense shadows were at first incorrectly interpreted as neoplastic metastases when in reality they were large healed tuberculous (probably primary) foci.

Case Reports

Case 1. E. L., male, aged 65, was admitted to Beth Israel Hospital in March 1932, complaining of abdominal pain, constipation, loss of appetite, and recent weight loss. Diabetes had been detected elsewhere a short time prior to admission.

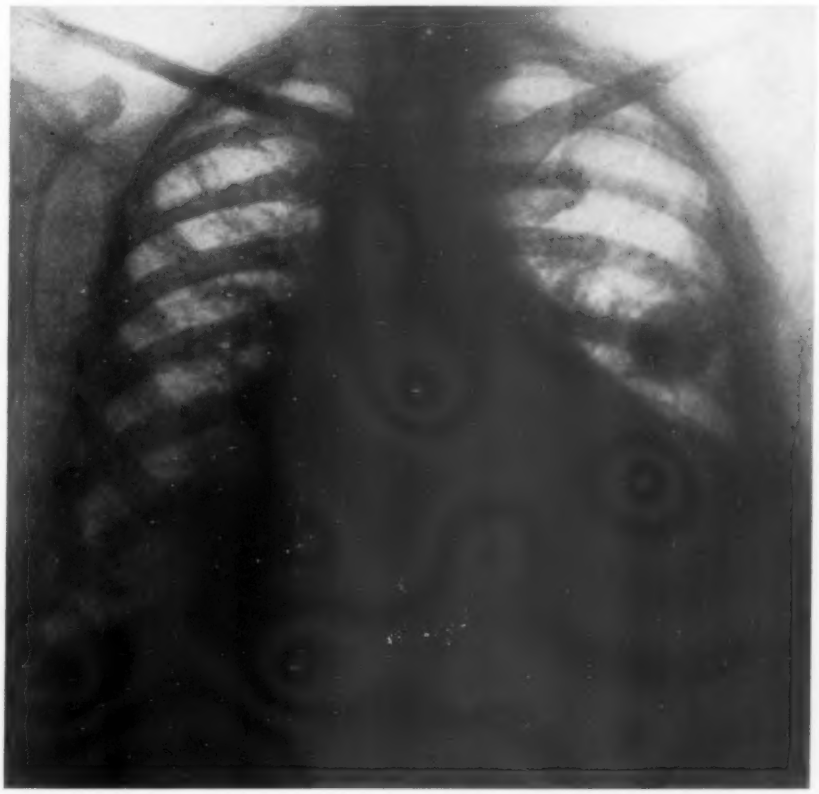

Fig. 1. *Case 1.* Roentgenogram showing shadow in the lower left lung field, first thought to be a metastasis from a carcinoma of the colon, actually a healed tuberculous focus.

On physical examination, the salient abnormal findings were confined to the cardiovascular system and to the abdomen, where a palpable mass was noted in the right upper quadrant. Laboratory studies, aside from the evidence of diabetes, showed nothing remarkable.

Satisfactory roentgen studies of the colon could not be carried out. A roentgenogram of the chest (figure 1) showed cardiac enlargement, and a round, dense, sharply circumscribed shadow in the lower left lung field. This was interpreted as a metastasis, probably from a carcinoma of the ascending colon.

The patient improved for a time and then symptoms of circulatory insufficiency appeared. The picture was further complicated by the development of cerebral symptoms, which were interpreted as being due to intracranial metastases. He died six weeks after admission.

Postmortem examination revealed severe occlusive changes in the coronary arteries with resultant myocardial damage. There was a large uriniferous cyst in the upper pole of the right kidney. In the lower portion of the left upper lobe of the lung a healed tuberculous focus measuring 3.2 cm. in diameter was found (figure 2).

FIG. 2. *Case 1.* Mass from lower lobe of left lung corresponding to shadow in figure 1. Note concentric ring-like arrangement, and the normal appearance of the surrounding lung tissue. This is most likely a healed tuberculous (probably primary) lesion. (Actual size.)

Grossly, this appeared to consist chiefly of whitish, firm tissue arranged in concentric rings. On microscopic examination, the same arrangement was seen, the layers consisting of hyalinized connective tissue, with occasional infiltration of lime salts No cellular structure or ossification was seen although numerous sections were examined. The surrounding pulmonary tissue appeared perfectly normal.

Comment: The combination of gastrointestinal complaints, abdominal mass, and round shadow in the lung led to the erroneous diagnosis of carcinoma of the colon with a pulmonary metastasis. As the necropsy showed, the mass was a uriniferous cyst and the pulmonary shadow represented a healed, probably primary, tuberculous focus (see below).

Case 2. M. K., male, aged 25, entered Beth Israel Hospital on August 5, 1930. Aside from a "cigarette cough" of many years' duration, he was perfectly well until five weeks prior to admission, when he suddenly became short of breath and expectorated a small amount of bloody sputum. The following day he had a chill which was followed by fever and expectoration of rusty sputum. A physician diagnosed pneumonia and treated him for the next two weeks, during which time the fever disappeared and the other symptoms diminished in intensity. One week later the fever recurred, and during the two week period preceding admission his temperature was intermittently elevated and there was expectoration of bloody foul sputum. The day before he entered the hospital he had a large hemoptysis.

On examination the temperature was 104° F. He was dyspneic and orthopneic and was expectorating large amounts of foul blood-tinged sputum. Over the lower

half of the left chest, there was impaired resonance, broncho-vesicular breathing, and moist râles.

A roentgenogram of the chest (figure 3) showed a large rounded mass in the lower left lung adjacent to the cardiac border. In the right midlung field a smaller, round, sharply circumscribed shadow was seen. The interpretation was a carcinoma of the left lung with secondary suppuration, and a metastasis to the right lung.

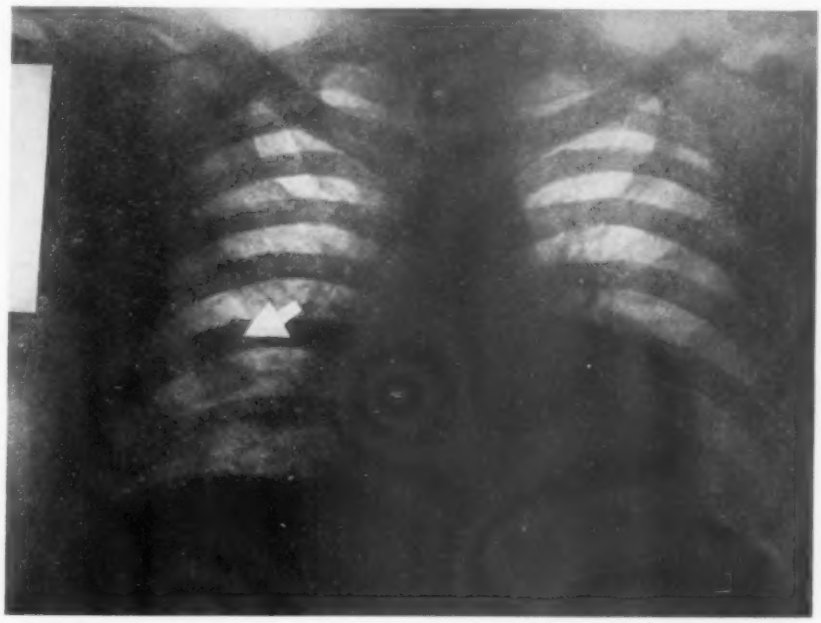

FIG. 3. *Case 2.* Roentgenogram on admission, showing paracardiac shadow in left lung due to abscess but first thought carcinoma. The shadow in the right lung (arrow) was first thought to be a carcinomatous metastasis.

After four days the temperature fell to normal and remained so thereafter. The expectoration diminished in volume and was no longer bloody or foul. Bronchoscopy on the twentieth day showed no abnormalities except for an odorless muco-purulent secretion from several branches of the left lower lobe bronchus. Roentgenograms of the chest showed gradual diminution in size of the shadow in the left lung; on the last two films there was cavity formation behind the heart shadow. The lesion on the right side remained unchanged.

The patient was discharged after a month and during a stay in the country made an uneventful recovery. When seen two and a half years later, he stated that he had remained free of symptoms. A roentgenogram of the chest (figure 4) showed no abnormalities other than the shadow in the right lung noted previously; this had not changed in size or density.

Comment: The clinical course indicated that the shadow in the left lung was due to a pulmonary abscess which later healed spontaneously, and not to a carcinoma as originally thought. The smaller shadow in the right lung, at first considered metastatic, failed to change in appearance in two and a half years and must therefore be regarded as a healed tuberculous focus, unrelated to the condition which brought the patient to the hospital.

Case 3. S. S., male, aged 55, came to the out-patient department of Beth Israel Hospital in September 1931. He had been treated by his physician for many years for a peptic ulcer but his symptoms had recently become more severe and had changed in character. Physical examination showed slight tenderness in the epigastrium and in the right upper quadrant but was otherwise negative.

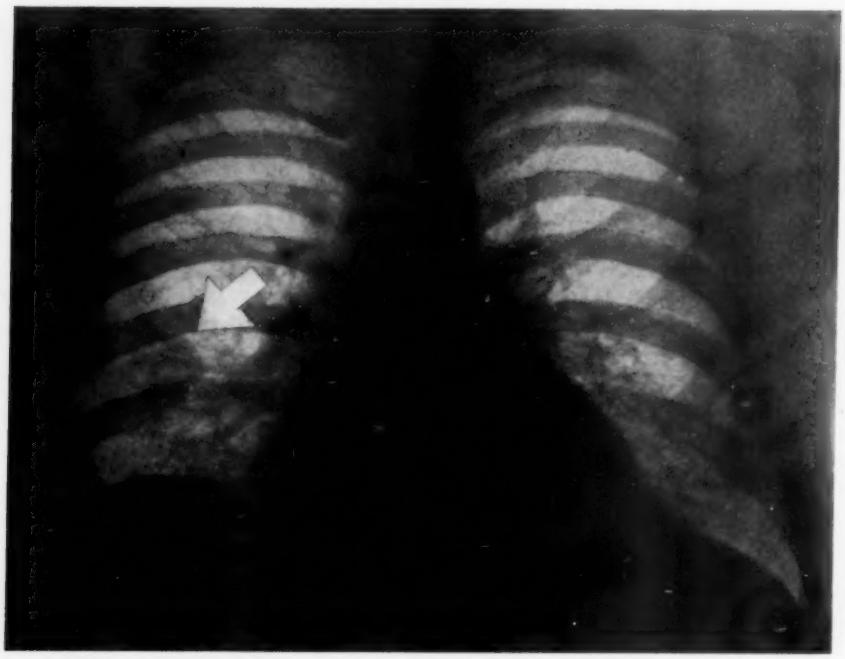

FIG. 4. *Case 2,* two and one-half years later. Note complete disappearance of abnormal shadow on left, while that in right lung (arrow) is unchanged.

Roentgen studies of the gastrointestinal tract showed an irregularity in the outline of the pylorus suggesting carcinoma. A roentgenogram of the chest (figure 5) showed a circular lesion about 2 cm. in diameter at the base of the right lung. This was regarded by the roentgenologist as probably a Ghon focus, but because of the gastrointestinal findings metastatic carcinoma was considered.

Operation was advised but the patient refused. He was placed on a Sippy regime and improved considerably. Because of a recurrence of symptoms 15 months later, new roentgen studies were made. Examination of the gastrointestinal tract showed the changes of a duodenal ulcer with periduodenal adhesions. In retrospect, the irregularity of the pyloric outline seen in the previous series which led to the suspicion of carcinoma was probably also due to adhesions. A roentgenogram of the chest showed the lesion previously noted to be unchanged in appearance.

Comment: As in case 1, the combination of symptoms and roentgen findings suggestive of disease of the gastrointestinal tract with the additional finding of a circular shadow at the base of the lung led to the erroneous diagnosis of carcinoma with a pulmonary metastasis. The benign clinical course over a period of 15 months served to rule out carcinoma.

The unchanged appearance of the pulmonary lesion during this time indicated that this was a healed tuberculous focus.

Case 4. B. G., female, aged 53, appeared in the out-patient department of Beth Israel Hospital in March 1933, complaining of severe sticking pains in the left side

FIG. 5. *Case 3.* Roentgenogram showing dense shadow in right lower lung field, first considered a possible metastasis from a carcinoma of the stomach. Subsequent films showed no change.

of the chest, arm, and upper abdomen of two months' duration. She was known to have had diabetes for five years. A tentative diagnosis of diabetic neuritis was made. A roentgenogram of the chest (figure 6) revealed a dense, rounded, sharply defined shadow at the left base. Since this shadow was regarded as a possible metastatic lesion, although the roentgenologist interpreted it as a Ghon focus, the patient was admitted to the neurological service for further study with a tentative diagnosis of secondary carcinoma of the spine.

Physical examination revealed no changes other than several diffuse neurological abnormalities. Laboratory studies showed nothing remarkable. Roentgen examination of the spine showed osteoarthritic changes in the lower thoracic region.

FIG. 6. *Case 4.* Roentgenogram showing shadow in lower left lung field representing a healed tuberculous focus but first considered a metastatic carcinoma. Subsequent films showed no change in size or appearance.

The patient was placed on a diabetic diet and given physical therapy. Her symptoms yielded readily to this treatment. Further roentgenograms of the chest showed no change in the appearance of the shadow, thus indicating that the original impression of metastasis was incorrect and that it was probably a healed tuberculous focus. She was discharged with the diagnosis of radiculitis due to osteoarthritis of the spine.

DISCUSSION

The discovery by roentgenogram of four examples of rather large solitary nodular infiltrations representing healed tuberculous foci within a relatively short period of time indicates that such lesions may not be very rare. Shanks, Kerley and Twining[10] show a picture of a large calcified shadow which did not change in appearance over a period of 14 years. Meyer[7] shows a photograph of a large tuberculous nodule simulating a metastatic lesion. Wessler and Jaches[12] state that "an early metastatic new growth especially when it is solitary, may closely resemble an incipient tuberculosis or a tuberculous infiltration may simulate a new growth. Error can usually be avoided by the clinical examination which will disclose a

primary growth and also by a later increase in the size and number of metastases."

In our four cases, the extra-pulmonary features contributed to the initial erroneous interpretation. In three of the four cases, the fact that the lesions did not change in size and appearance over a prolonged period of observation served to establish the correct diagnosis. In the fourth case, the life of the patient (case 1) was terminated by an unrelated condition and the correct interpretation was then indicated by the necropsy findings.

The interpretation of the pathological findings warrants some discussion. As described above, the nodule in the lung presented a lamellated appearance both on gross and microscopic examination; calcific deposits were found between some of the layers. These findings are consistent with the description of healed primary tuberculous lesions as given by Pagel and Henke.[9] Moreover, these authors state that the presence of lung tissue free of atelectasis or inflammation immediately surrounding the nodule points to a healed primary, rather than post-primary, lesion. Areas of ossification, which, when found, are pathognomonic of a healed primary focus were not seen. A careful search of the section on pulmonary affections in Henke and Lubarsch's treatise on Pathology failed to reveal any other condition in which the lesion resembled the one in our case. It seems reasonable to state, therefore, that this nodule was a healed tuberculous, most likely primary, focus. Incidentally, it is one of the largest specimens of this lesion which we have been able to find on record.

Not only must healed tuberculous foci be differentiated from metastatic lesions which are usually asymptomatic but occasionally primary pulmonary neoplasms, either malignant or benign (such as chondroma, fibroma, and lipoma), must be ruled out. In view of the current trend toward operation in these cases, such differentiation is of the utmost importance. In a recent article by Graham and Singer,[4] three cases were reported in which calcified pulmonary masses were resected on the basis of the diagnosis of tumor. In one of these (case 2) there were no pulmonary symptoms. In at least two of their cases the specimens as shown in photographs resemble our specimen and are highly suggestive of healed tuberculous foci.

Hirsch [5] has described sharply circumscribed, dense spherical shadows in cases of polycythemia vera. On the basis of a single roentgen examination they were similar to those noted in our cases. However, in polycythemia, the lesions began to fade after they reached a certain density and completely disappeared, the entire cycle usually lasting about three weeks. This evolution as well as the clinical features should serve to differentiate the lesion from a healed tuberculous focus.

Summary

Four cases are described in each of which a fairly large, dense, rounded, sharply circumscribed solitary shadow was noted in a roentgenogram of

the chest. In each case there were additional clinical and roentgen findings to suggest that these lesions were metastatic from a primary carcinoma elsewhere in the body. In one case necropsy showed a large mass, characteristic of healed tuberculosis, probably primary, and no evidence of a malignant lesion. In the other three cases the clinical course failed to bear out the diagnosis of carcinoma. In these cases the pulmonary shadows observed over a considerable period did not change in size or appearance, indicating the correct interpretation of healed tuberculous foci.

Addendum: Since this paper was submitted for publication, we have seen a patient with carcinoma of the sigmoid colon in whom a roentgenogram of the lungs showed two healed tuberculous foci, at first considered metastatic lesions.

In each of two recent papers (HAIGHT, C. and FARRIS, J. M.: Tuberculoma of the lung, Jr. Thorac. Surg., 1939, ix, 108–116; JONES, J. C. and DOLLEY, F. S.: Lobectomy and pneumonectomy in pulmonary tuberculosis, Jr. Thorac. Surg., 1939, viii, 351–370), there are reports of lobectomy for tuberculoma.

We wish to thank Drs. A. A. Epstein, E. D. Friedman, and I. W. Held for permission to report cases from their respective services. We should also like to express our appreciation to Dr. I. Seth Hirsch for aid in interpreting the roentgenograms, to Dr. A. Plaut for his study of the necropsy material in case 1, and to Dr. H. Wessler for valuable criticism.

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THE HIPPURIC ACID TEST IN HYPERTHYROIDISM *

By Samuel F. Haines, M.D., F.A.C.P., Thomas B. Magath, M.D., F.A.C.P., and Marschelle H. Power, Ph.D., *Rochester, Minnesota*

For many years it has been known that disturbances in the function of the liver might occur in severe exophthalmic goiter. Jaundice has been recognized to be a serious, and usually late, development in the crisis of exophthalmic goiter.

In cases of this type livers have frequently showed changes designated by Robertson [1] as "subacute yellow atrophy." In 1933, Weller [2] found a patchy, chronic parenchymatous, interlobar hepatitis in many of the livers of patients with exophthalmic goiter. In the same year, Beaver and Pemberton [3] studied the livers of 107 patients with exophthalmic goiter and found acute degenerative lesions, simple atrophy, or subacute toxic atrophy and toxic cirrhosis in a high percentage of their cases. They expressed the opinion that these changes were a part of the syndrome of exophthalmic goiter and were related to the severity of the disease. Kuriyama, in 1918,[4] found that the feeding of thyroid to animals was followed by a rapid loss of glycogen from the liver.

Functional Tests

Hepatic functional tests have been studied in hyperthyroidism in recent years. Sanger and Hun,[5] as a result of studies of glucose utilization in hyperthyroidism, concluded that in this disease there is probably a failure of storage of glucose in the liver, due to a toxic change in the liver caused by the disease. In 1926, Youmans and Warfield,[6] studying the liver function by the phenoltetrachlorphthalein test as well as other tests, found impairment of liver function indicated by the tests in 50 per cent of their 44 cases. They found a relation between the impairment of liver function and loss of weight. Bartels,[7] using the hippuric acid test of Quick,[8] studied 148 cases of hyperthyroidism, and found a normal response to this test in only 18 cases. He concluded that the results of the test indicate a degree of change in liver function in direct relation to the severity of hyperthyroidism, but found absence of weight loss or a history of previous iodine medication in patients with a normal liver function as measured by the test on admission. The liver function improved after preoperative treatment in exophthalmic goiter cases, and was usually normal three months after thyroidectomy. A high carbohydrate diet apparently caused improvement in some cases. Recently Quick [9] has described a method for doing the hippuric acid test by the intravenous injection of 1.77 gm. of sodium benzoate and the determination of hippuric acid excretion in the urine in the hour following the injection.

* Submitted for publication August 11, 1939.

Present Study

In an attempt to determine whether or not the hippuric acid test would be of value in the handling of patients with hyperthyroidism, and whether or not it could give any information regarding the pathologic physiology of this condition, the test has been carried out in 17 cases of adenomatous goiter with hyperthyroidism and 61 cases of exophthalmic goiter. In the first group, nine of the 17 cases were tested by the oral method, and in the latter group, 42 cases were tested by the oral method. In the other cases, the intravenous test was used. In the few cases in which both methods of testing were used, comparable results were obtained by the two methods. In doing the test by the oral method the urine was collected for four hours after the oral administration of 6.0 gm. of sodium benzoate. In doing the test by the intravenous method 1.77 gm. of sodium benzoate were injected intravenously and the urine was collected for one hour after that. The hippuric acid in the urine was determined in either case by the method of Griffith.[10] Normal results stated by Quick are, for the oral method, 3.0 gm. of benzoic acid (equivalent to 4.41 gm. of hippuric acid) and, for the intravenous method, 0.7 to 0.95 gm. of benzoic acid (equivalent to 1.0 to 1.4 gm. of hippuric acid). Tests done on patients with cardiac decompensation or known urea retention are not included in this study.

Correlation with Bromsulfalein Test

Snell and Plunkett,[11] using the hippuric acid test (oral) in patients with liver disease and comparing it with other tests of hepatic function, found that the synthesis of hippuric acid is a reasonably accurate and satisfactory test for the determination of parenchymatous hepatic damage. They concluded that the excretion of 1.5 gm. or less of hippuric acid is probably indicative of severe damage to the hepatic parenchyma. We have done both the bromsulfalein test and the hippuric acid test either orally or intravenously in 22 cases of hyperthyroidism, 19 of them cases of exophthalmic goiter. An attempt was made to do the tests as closely together as possible; in the majority of instances they were done on consecutive days. The results are noted in table 1. It is to be noted that very low hippuric acid output may occur in the absence of dye retention, but that in all cases with dye retention greater than grade 1, on the basis of 1 to 4, there was some reduction of hippuric acid output. This would add to Quick's and Snell and Plunkett's evidence that hepatic lesions have an influence on the rate of synthesis of hippuric acid in human beings.

Correlation with Basal Metabolic Rate

There is no constant and accurate criterion of the severity of hyperthyroidism; however, in a large group of cases the height of the basal metabolic rate will correlate reasonably accurately with the severity of the disease, and as this is our most accurate estimate that can be expressed

TABLE I

Comparison of Bromsulfalein Test and Hippuric Acid Test

	Bromsulfalein retention, grade *	Hippuric acid, gm. (oral)	Hippuric acid, gm. (intraven.)
	0	1.1	
	0	2.9	
	0	3.0	
	0	3.1	
	0	3.3	
	0	3.4	
	0	3.7	
	0	4.2	
	0		0.7
Exophthalmic goiter	0		0.3
	1	2.5	
	1	4.4	
	1	5.0	
	2	1.9	
	2	2.8	
	3		0.4
	4	0.5	
	4	1.4	0.5
	4	1.7	
Adenomatous goiter with hyperthyroidism	0		0.3
	0	3.8	
	1	2.8	0.6
Low basal metabolic rate	1	4.5	

* On a basis of 1 to 4.

numerically, the outputs of hippuric acid have been compared with the basal metabolic rates. The results are best expressed in figure 1. The average hippuric acid output with the oral test in patients with basal metabolic rates of less than + 40 per cent is 3.42 gm. while in those with basal metabolic rates of + 40 per cent or greater it is 2.85 gm. of hippuric acid. When the test was done by the intravenous method the average was 0.98 gm. in the first group and 0.95 gm. in the second. It is to be noted that many patients with only slight elevations of the basal metabolic rate had reduced outputs of hippuric acid. These were not in all cases patients who had been seriously ill before coming to The Mayo Clinic. In some instances very low outputs of hippuric acid were encountered in young patients with exophthalmic goiter of moderate intensity and very short duration. However, there is, in general, a slight negative correlation between the severity of hyperthyroidism and the output of hippuric acid. This fact was first noted by Bartels.

We question the significance of hippuric acid outputs of 3 gm. or more when the oral test is done. Only 16 out of 41 patients with exophthalmic goiter had hippuric acid outputs less than this figure.

WEIGHT LOSS AND DURATION OF HYPERTHYROIDISM

In our cases we found no correlation between loss of weight and hippuric acid excretion. In one instance in which no weight had been lost the oral

intake was followed by excretion of only 0.9 gm. of hippuric acid. Weight losses of 52 and 60 pounds were noted in patients with normal hippuric acid outputs.

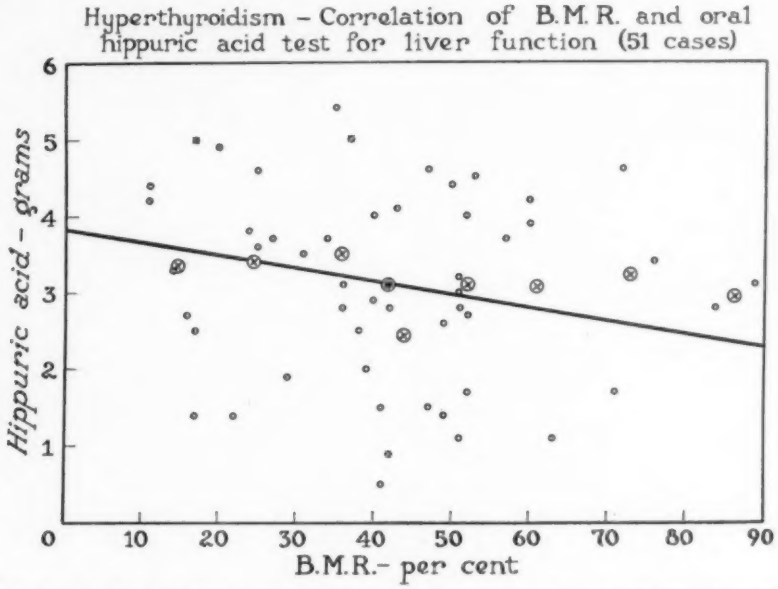

FIG. 1. Correlation of basal metabolic rate and the results of the oral hippuric acid test.

Our findings agreed with Bartels' in finding no correlation between hippuric acid excretion and the duration of hyperthyroidism. The average hippuric acid excretion in cases of exophthalmic goiter of a duration of one year or less is 3.13 gm. whereas in those with a duration of more than one year it was 3.05 gm. No statistically significant variation could be found in this regard. Inasmuch as the duration of hyperthyroidism is so important in relation to surgical risk of thyroidectomy, it would seem that this test does not indicate the deciding factor in this regard.

VITAMINS

Recent work indicating vitamin deficiency [12] in hyperthyroidism and showing regeneration in the liver glycogen and gain in weight in hyperthyroid animals given B_1 and B complex [13] suggested the desirability of investigating the possible effect of these vitamins on the hippuric acid excretion. It was necessary to limit the time of administration of the vitamins used to the usual period of preoperative preparation, and it was necessary to give all the patients Lugol's solution during that time. Those patients to whom vitamin B was given received 9.9 mg. of thiamin chloride daily except one patient who received 200 mg. of thiamin chloride intravenously in a period of six days. There was a tendency toward increase in the hippuric acid excretion in most cases during the period of treatment. This improvement corre-

sponded closely to the improvement noted with Lugol's solution alone. Two patients, both severely hyperthyroid for many years, and both having markedly reduced hippuric acid excretion, were given thiamin and brewers' yeast over periods of four and six weeks without change in the hippuric acid excretion in one case, and in the other, with only slight improvement of the degree frequently seen after administration of iodine. The possible effect on hippuric acid excretion of vitamins given over longer periods of time should be determined.

Glycine

Quick reported an increase in the output of hippuric acid when glycine is given to the patient. In an attempt to determine whether the reduced excretion found in these patients was due to a lack of available glycine or failure of conjugation of glycine and benzoic acid, eight patients were given glycine in doses of 4 to 8 gm. three times a day for two to three days, and, immediately after a single dose of 8 gm., the test was repeated. The results were not consistent, and further study will have to be made to determine the reason for this. The results of glycine administration are shown in table 2.

Table II

The Effect of Glycine on the Hippuric Acid Test

B.M.R. %	Weight loss (lbs.)	Hippuric acid, gm.		Method	Dye test (retention, grade*)
		Before glycine	After glycine		
+47	47	1.5	1.4	Oral	
+49	49	2.6	3.1	Oral	
+36	25	2.8	5.4	Oral	
+39	31	2.0	5.2	Oral	
+51	27	3.2	3.5	Oral	
+78	60	0.3	0.7	Intravenous	
+60		0.7	0.5	Intravenous	3
+91		0.3	1.0	Intravenous	0

* On a basis of 1 to 4.

The reason for the failure of an increase in the hippuric acid output after the administration of glycine in two cases, and the slight increase in two others, is of interest. Whether this phenomenon is due to failure of absorption of glycine, lack of ability to conjugate glycine and benzoic acid, or rapid metabolism of the administered glycine cannot be said at present.

The continuance of the use of glycine in some of these cases, as well as some others not reported here, did not result in any determinable clinical improvement.

Comment

The reduction of hippuric acid excretion occurs in a significant number of patients with hyperthyroidism. There is some correlation between the

hippuric acid output and the results of the bromsulfalein liver function test, corroborating the opinions of other investigators that hippuric acid formation is related to liver function. Although there are wide variations, there is some correlation of the results of this test with the basal metabolic rate, the tendency being toward a lower hippuric acid output as the basal metabolic rate rises. No significant correlation could be found between the hippuric acid test and loss of weight, duration of hyperthyroidism, or the administration of vitamin B_1. Preoperative treatment with iodine and whatever supplementary treatment seemed indicated resulted in slight improvement in the test in most cases.

Marked reductions in hippuric acid excretion were found in a few cases of the type long designated by H. S. Plummer [14] as having vital organ degeneration. Pigmentation of the skin is usually a feature of these cases. Ordinarily the surgical risk in such cases is high, and prolonged periods of preoperative treatment are advisable in order to allow opportunities for recovery from visceral damage. The occurrence of significantly low tests in such cases might suggest that the test could be helpful in classifying some cases as needing prolonged preoperative treatment. However, we have found as low tests in young patients with exophthalmic goiter of short duration in whom the usual period of preparation was followed by no unusual reaction. A rising hippuric acid excretion has, in two such cases, been concomitant with a general clinical improvement of the type which, by our usual criteria, has indicated to us that the patient was reaching a status in which operation could be performed relatively safely. In both cases thyroidectomy was done without incident and was followed by no unusual reaction.

In one patient a marked reduction in hippuric acid excretion remained constant throughout a prolonged period of preoperative treatment. A severe reaction characterized by gradually rising temperature and pulse and marked prostration resulted in death 48 hours after operation. The reaction was that usually seen in patients who have had hyperthyroidism for many years. Marked hepatic damage was found at autopsy.

However, we have been unable to show any consistent correlation between hippuric acid excretion and any status which is judged serious on the basis of our present criteria. We do not feel, therefore, that the test can be given a position of importance in the handling of patients with hyperthyroidism. The clinical judgment of visceral damage and of high surgical risk is, as a matter of fact, reasonably accurate, and the criteria for establishment of this judgment are reasonably clear. The test continues to be of interest to us, however, because of its implications regarding the pathologic physiology of the liver in hyperthyroidism, and from this angle further study is desirable. Boyce [15] has cautioned that the " test should not be assumed to tell more than it is supposed to tell," stating that it only interprets liver damage in terms of liver function. It seems probable that marked alterations in this test can occur because of functional changes in the liver that must be of short

duration, and temporary. It is important to remember that our conclusions have only to do with the use of this test in hyperthyroidism in the absence of jaundice and that no suggestions are made here regarding the value of the test in obstructive jaundice.

Conclusions

The excretion of hippuric acid in Quick's test is reduced in a significant number of cases of hyperthyroidism. This is in agreement with the opinion held in recent years that the liver is frequently functionally disturbed in hyperthyroidism.

Reduction of the excretion of hippuric acid is correlated inversely to a slight degree with the basal metabolic rate.

Excretion of hippuric acid is usually diminished when the bromsulfalein test shows retention of dye and is also decreased in some other cases.

The excretion of hippuric acid is not uniformly reduced in patients, who, by other criteria, may be assumed to have a high surgical risk, nor do all patients with marked reduction in excretion of hippuric acid present other criteria suggesting high surgical risk. This study would not indicate, therefore, that the test is of great value in management of hyperthyroidism. The test cannot replace any factor of clinical judgment in regard to hyperthyroidism.

Further study of the physiologic implications of this test in hyperthyroidism should be carried out.

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PSYCHOSIS IN HYPOPARATHYROIDISM; WITH A REPORT OF FIVE CASES *

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Psychosis is not mentioned as a complication of parathyroid tetany in the usual texts of medicine and in the systems of medicine it is briefly referred to as being very rare. It has been known since 1852 that psychosis may occur in tetany and the subject was reviewed in 1907 by Frankl-Hochwart [1] and in 1920 by Barrett.[2] In a recent report Barr, MacBryde and Sanders [3] mention that psychosis may occur in parathyroid tetany, but they do not state the frequency. It is practically impossible to ascertain the incidence of parathyroid deficiency in the cases of psychosis and tetany described in the older literature. The fact that we have been able to find only four cases reported in the literature [4] during the past 19 years supports the idea that this complication is very rare. On the other hand, five of the 18 patients with hypoparathyroidism observed at the University Hospital during the past nine years have developed a psychosis. Such a high incidence in this Clinic suggests that the complication occurs more frequently than is generally appreciated.

It appears, therefore, that the occurrence of this complication should be emphasized, that additional cases should be reported, and that certain of the clinical aspects should be discussed.

Case Reports

Case 1. L. F., a white married woman, 34 years of age, entered the University Hospital, March 10, 1922, because of hyperthyroidism. She recovered following a partial thyroidectomy without complications and was sent home 10 days later. She returned November 11, 1929, for a recurrent hyperthyroidism and developed tetany on the fifth day after a subtotal thyroidectomy. The manifestations were partially controlled with calcium lactate orally and she went home to continue this therapy. The symptoms of tetany soon increased and she returned to the hospital April 2, 1930. She was found to have chronic tetany but there were no obvious mental disturbances. She stated, however, that her sexual desires had increased beyond her control and her husband later stated that she had "acted queerly" since her operation. During the sixth day in the hospital she became irritable, exhilarated, talkative, and erotic. Delusions and hallucinations developed and a few hours later she became drowsy and semicomatosed. The periods of excitation alternated with those of drowsiness and each usually persisted for several hours. The serum calcium returned to normal 8 days after parathyroid extract and calcium therapy were begun, but the psychosis was unaltered until two weeks later when it began to subside gradually and did not entirely disappear until one month later. She was sent home to continue the above therapy, but it was soon discontinued. Tetany persisted for five years before she developed cataracts which caused her to return to the hospital in August 1936. The serum

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calcium was 4.6 mg. per cent at this time, but there were no mental abnormalities nor had there been any since the previous admission.

Case 2. A single white woman, 35 years of age, entered the University Hospital in September 1929, because of a large, nontoxic nodular goiter. Tetany did not develop following a partial thyroidectomy 13 years previously, but it appeared four days after the subtotal thyroidectomy in 1929. The manifestations were partially controlled with calcium salts and parathyroid extract. She returned home on calcium therapy alone. The symptoms reappeared, however, and she reëntered the hospital December 17, 1929, in a confused mental state. She refused to talk and she was hyperactive. Delusions and hallucinations developed during the next six days and the periods of hyperactivity alternated with those of drowsiness in which she was semi-comatosed. The psychosis steadily progressed until five days after the serum calcium had been brought to normal with parathyroid extract and calcium salts. There was then a gradual improvement requiring approximately one month for complete recovery. Continuation of the above treatment was recommended at the time of her discharge, but she did not consistently follow this advice and returned to the hospital several times in chronic tetany until 1938. There had been no recurrence of the psychosis during the interval of eight years of chronic tetany.

Case 3. A white married woman, 44 years of age, entered the University Hospital March 8, 1933, because of hyperthyroidism. Parathyroid tetany developed 10 days after subtotal thyroidectomy. Mental confusion, hallucinations, extreme anxiety, and delusions of persecution appeared during the following six days and suicide was attempted. The psychosis continued until 13 days after the serum calcium had been brought to normal with calcium salts and parathyroid extract therapy. There was then a gradual improvement for three weeks but at this time confusion and delusions reappeared and suicide was again attempted. Hyperactivity became so extreme that it became necessary to restrain the patient for several days. Improvement was rapid for the next five days and she was able to return home although the psychosis had not subsided entirely.

Case 4. A white, married man, 45 years of age, entered the University Hospital, May 16, 1934, for parathyroid tetany. The tetany had appeared four days after a subtotal thyroidectomy five months previously. The symptoms had been controlled with parathyroid extract, but he had objected to the hypodermic injections and had omitted them. Chronic tetany was found to be present and the serum calcium was 6.8 mg. per cent. The second day in the hospital before treatment was instituted he became restless, refused to eat or drink, began to moan and groan, developed fecal and urinary incontinence, became excited, and developed sexual hallucinations. Convulsions and carpopedal spasm were conspicuous by their absence. Parathyroid extract and calcium therapy were then begun, and eight days later the serum calcium had reached normal. The psychosis, however, increased during this time and continued unaltered for another eight days. This was followed by a gradual improvement which required 30 days before the mental status was regarded as normal. He returned home with instructions to continue the above therapy, but did not follow the advice and was readmitted to the hospital six months later in chronic tetany. He denied having had any mental disturbances since his last visit and there were no evidences of psychosis at the time of this examination.

Case 5. A white widow, 63 years of age, entered the University Hospital, April 24, 1938, because of recurrent hyperthyroidism. On the fifth day following the subtotal thyroidectomy she became depressed, refused to eat, and developed delusions. During the next nine days she became delirious and attempted suicide. Another 10 days elapsed without alteration in the mental symptoms when she began to have convulsions. At this time the presence of parathyroid tetany was recognized. The convulsions ceased two days after institution of calcium and dihydrotachysterol therapy although another 14 days passed before the serum calcium had risen to normal.

During this time the psychosis improved remarkably, but three days later convulsions reappeared and the psychosis became aggravated to its previous intensity. The serum calcium was found to be 13.0 mg. per cent. The above therapy was then discontinued and convulsions ceased two days later. The psychosis, however, persisted for another five days and subsided gradually, requiring 35 days to completely disappear.

Comment

The usual type of psychosis which accompanies parathyroid tetany is a toxic delirium, although other types including actual dementia have been described. It is generally agreed that there is no specific type of psychosis in tetany. The following symptoms: anxiety, depression, and a sense of impending disaster are common, but they are rarely of sufficient intensity to be classified as a psychosis. Our cases are typical examples of a toxic delirium in which delusions and hallucinations developed. Sexual hallucinations were present in two of our cases (1 and 4) and in both instances the sexual drive had been greatly augmented previous to the appearance of the psychosis. Delusions of persecution also occurred in two cases (3 and 5) and suicide was attempted in both instances.

It appears that if a psychosis is going to occur in parathyroid tetany, it will develop during the first three or four months of the disease. It may appear the first few days postoperatively (Cases 3 and 5) or it may not develop for several weeks (Cases 1, 2, and 4). Psychic disturbances may be the first and only manifestation observed and the patient's condition may be misapprehended unless the possibility of parathyroid tetany is considered and search is made for the other manifestations, namely, Chvostek's and Trousseau's signs, and the serum calcium level (Case 3). Carpopedal spasms and convulsions are not necessarily present during the psychosis, in fact, they are usually absent (Cases 1, 2, 3, and 4).

The prognosis in the psychosis is usually good. The psychic manifestations may be present only temporarily during and following a convulsion or they may persist for several months. There is usually a delay in the response of the mental condition of from one to four weeks after the serum calcium reaches normal and then another three or four weeks are required for complete recovery. The mental symptoms persisted for several months after successful treatment of parathyroid tetany in the two cases reported by Knospe [4c] but both patients had a previous psychosis during the hyperthyroidism and this fact may account for the longer duration of the psychic disturbances in his patients.

A psychosis is not likely to recur if it has definitely subsided even though tetany returns. Cases 1, 2, and 4, of our series were observed for 6 and 8 years and 6 months respectively after the psychosis had subsided, and after return of the tetany without a return of psychic disturbances. Organic cerebral changes occur undoubtedly in cases of dementia associated with tetany, but the importance of tetany as an etiologic factor in the production of such alterations is questionable. It was suggested by Barr, MacBryde and Sanders [8] that edema of the cerebrum and meninges may be a contributing

factor in producing cerebral and psychic manifestations after they had observed two patients with papilledema and an increase in intrathecal pressure. The calcium content of the cerebrospinal fluid was normal in their cases, whereas the serum calcium was low. Such circumstances were said to be favorable for the production of edema of the brain. Gregory and Andersch [5] had previously shown that the calcium content of the cerebrospinal fluid did not necessarily coincide with that of the blood serum. The calcium content of the cerebrospinal fluid was not measured in any of our cases, but the intrathecal pressure was normal in three (Cases 2, 4, and 5) when measured several times during the psychosis and several careful ophthalmoscopic examinations during the psychic disturbances in each of our cases revealed no papilledema. Careful neurologic examinations showed no persistent manifestations of organic central nervous system lesions in any of our cases.

The factors which produce the psychosis are not known. The fact that it occurs comparatively early in the tetany and that it does not recur, although the parathyroid deficiency may relapse, suggests that it is due to failure of adjustment of the cerebrum to the acute chemical changes. Such a hypothesis is supported by the great aggravation of the psychic manifestations in Case 5 during the occurrence of hypercalcemia. Against such a theory is the delayed response of the psychic disturbances as compared to the chemical response to adequate therapy.

Summary

Parathyroid tetany is complicated by psychosis more commonly than is generally appreciated. The complication occurred in 5 of 18 cases, and these 5 cases are reported. The psychic disturbances are usually of the toxic delirium type, occurring during the first few months, and may be the only obvious manifestation of tetany. The prognosis is good and it is not likely to recur although the parathyroid deficiency may relapse. The response to adequate treatment is slower than are the other manifestations of tetany and three or four weeks or several months may elapse after adequate control of the tetany before the psychosis subsides.

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CARDIAC ADAPTATIONS IN ACUTE PROGRESSIVE ANOXIA *

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Circulatory Reactions in Man

The reactions of the cardiovascular system in man to progressively diminishing oxygen have been repeatedly described, among others by Whitney,[1] Schneider,[2] Schneider and Truesdell,[3] Gellhorn,[4] and Armstrong.[6] While there are variations assignable to individual sensitivity, speed in development of anoxia, etc., the following reactions commonly occur in standard rebreathing tests: The heart rate increases, systolic pressure rises slightly and diastolic pressure either remains stationary or changes slightly in upward or downward directions. A dynamic analysis of such data indicates that the diminishing oxygen-carrying capacity of the blood is compensated by increased circulating volume as well as by the greater pulmonary ventilation.

However, initial studies of the human circulation by methods applicable to man yielded but little evidence that the circulating volume increases during anoxia. Thus Schneider and Truesdell [3] reported that capillary flow seems to be retarded, that venous pressure falls and that the volume of blood flow through the hand decreases. Subsequent investigators [7] reported somewhat variable results. Estimations of cardiac output by gasometric methods [8] either gave no indications of significant changes or indicated a slight tendency toward a decrease. It now appears that the early applications of gasometric methods were not reliable and that the difficulty of using them during anoxic states had not been mastered. Now, authorities [5, 9] seem to be in agreement that an increase in cardiac minute output plays an important rôle in anoxia and in acclimatization to high altitudes.

Analysis of Reactions in Dogs

The manner in which such compensatory increase in cardiac minute output occurs cannot be satisfactorily analyzed by studies limited to man. Fortunately, as Sands and De Graff [10] first showed, the cardiovascular reactions during progressive anoxia are essentially the same in dogs, lightly anesthetized by non-volatile anesthetics. It is, therefore, logical to transfer to man other discoveries which could only be made by procedures involving operative technic and the use of refined cardiodynamic apparatus applicable only to animals.

What I shall review consists essentially of some contributions from our own laboratory, reinterpreted, in some instances, in the light of other discoveries which have given them new or added practical significance.

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When a lightly anesthetized dog rebreathes air from which oxygen is being continually removed by the body and CO_2 by soda lime, the content of oxygen in the respired mixture decreases evenly from 20 to 5 per cent. The rapidity of the decrease depends upon the size of the respirator used. Figure 1 shows such effects during the course of 90 minutes.

Hypoxia and Anoxia

In interpreting the cardiovascular reactions in such tests it is important to orient ourselves regarding the degree of oxygen deficiency which exists during successive intervals of rebreathing and to determine clearly the stage at which significant oxygen-lack manifests itself. A regularly decreasing percentage of oxygen in the inspired air, as indicated by line 0, is not equivalent to an even rate of theoretical ascent to higher altitudes (line A) nor to an even progression of the oxygen deficiency indicated by the calculated oxygen saturation of arterial blood (line HbO). Thus, as shown in figure 1, the animal at the end of the first 40 minutes is at a theoretical elevation of 11,000 ft. and the oxygen saturation or arterial blood has decreased approximately from 20 to 17.8 volumes per cent. During the next 20 minutes partial pressure of oxygen corresponds to an altitude of 19,000 ft. and the blood saturation decreases as much again, i.e., to about 14.5 volume per cent. It is somewhere during this stage—the exact point varying somewhat in different animals—that a significant state of anoxia first exists when an animal is at rest. Beyond this time the blood oxygen decreases more and more rapidly so that after the next 20 minutes it has a value of only 9 volumes per cent and the effects of anoxia become critical for the heart and circulation.

From the viewpoint of cardiac physiology, as established by animal experiments, we may divide the effects of diminishing oxygen lack into two phases, conveniently distinguished by the terms hypoxia and anoxia. In figure 1, the line is arbitrarily drawn at the end of 50 minutes, when the percentage of oxygen rebreathed has been reduced to about 12 per cent, corresponding approximately to the altitude of Pike's Peak. I believe this corresponds roughly, also, to a degree of oxygen deficiency tolerated temporarily, without significant symptoms, by the majority of humans, provided they remain at rest. It must be remembered, however, that any muscular activity, at any elevation, adds significantly to the degree of oxygen deficiency, due to reduced oxygen pressure alone.

Cardiovascular Reactions During Hypoxia

By recording carotid pressures by means of calibrated optical manometers, Sands and De Graff [10] showed that significant changes occur during the stage of hypoxia. As indicated graphically in figure 1, the heart accelerates considerably, systolic pressure rises significantly, and usually diastolic pressure as well. Concurrently, *effective venous pressure* tends to decrease somewhat. In short, the cardiac and circulatory changes must be considered anticipatory

to the time when serious oxygen deficiency occurs, and generally precede compensatory respiratory changes which do not become significant until true anoxia begins to develop.

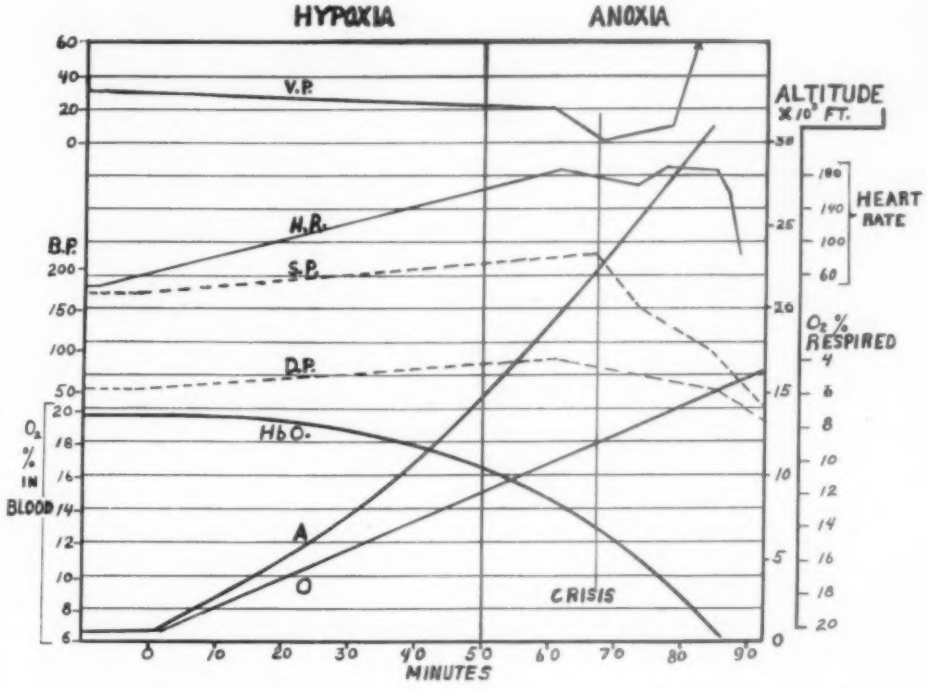

FIG. 1. Graph showing relation of percentage oxygen respired (O) to altitude (*A*) and oxygen saturation of blood (HbO) and division into stages of hypoxia and anoxia. Smoothed curves showing trend of reactions of heart rate (H.R.), venous (V.P.), systolic (S.P.) and diastolic (D.P.) pressures in dogs during progressive hypoxia and anoxia.

The cardiac acceleration, which is much greater than in similar rebreathing tests in man, is the dominant reaction during the stage of hypoxia. It is due chiefly to progressive reduction in vagal tone, for acceleration is slight if the animals have been previously vagotomized. The fact that some increase in heart rate still occurs, together with the marked decrease in the systole/cycle ratio in normal animals, strongly suggests that sympathetic stimulation or some other adrenergic action is also involved (Sands and De Graff [10]).

When changes in cardiac output are recorded in "open-chest" dogs by placing a cardiometer around the ventricles, the changes that occur during progressive rebreathing are not always consistent. The stroke volume decreases; but the calculated minute output may show either an increase or a decrease. We shall discuss this matter later. Oncometer studies have shown that the limbs and kidneys generally increase in size, while the spleen volume diminishes. The blood flow through various portions of the brain

increases. These changes indicate that a redistribution of blood flow occurs, probably due to reciprocal vasomotor actions.

I have made calculations of the total peripheral resistance during hypoxia, using the formula $R = \frac{Pm \times 1332}{Vt} = \frac{\text{dynes} \cdot \text{sec.}}{\text{cm.}^5}$. In this equation, *Pm* denotes mean pressure in mm. Hg, Vt., the cardiac output per sec. Such calculations invariably indicate that the total resistance to "run off" from the aorta is decreased during hypoxia. However, recent studies [12] make it questionable whether such deductions are allowable, because they do not evaluate possible active changes in the diameter and elasticity of the aorta. Similarly, the magnitude of vasomotor changes cannot be estimated quantitatively by actual or percentile changes in mean pressure, as is commonly done.

The slight decline of venous pressure has been interpreted as indicative of changes in the peripheral circulation and a reduced venous return to the heart. This has not been demonstrated, and it is equally probable that it is due to the greater minute output of the heart.

Cardiovascular Changes During Anoxia

During the much briefer stage of true anoxia, as defined above, the acceleration of the heart has nearly reached a maximum. Consequently, other compensatory reactions must occur if the minute output is to increase further. The question whether oxygen deficiency at this or earlier stages exerts an initial stimulating action on the ventricles prior to its late depressant action has generally been answered negatively. I have already called attention to my own cardiometer experiments indicating that the stroke volume decreases; *but* whether such decrease is greater or less than would be anticipated in accordance with Y. Henderson's law of cardiac behavior is difficult to determine from such experiments. Most laboratory investigators, among them Mathison,[13] Doi,[14] Gremels and Starling,[15] Jarisch and Wastl,[16] conclude that oxygen has no stimulating action on the ventricles, but that dilatation and depression result when blood is about half-saturated with oxygen.

With these conclusions, observations in our laboratory do not agree. Sands and De Graff,[10] recorded left ventricular and aortic pressure curves by optical manometers, in vagotomized dogs. In experiments in which heart rate and diastolic aortic pressure did not change, the ventricular pressure curves indicated the uncomplicated responses of the myocardium to decreasing oxygen. A few segments of such records are reproduced in figure 2. During hypoxia, no significant changes are found. As anoxia develops, the ventricular pressure curves (lower records) exhibit a more rapid gradient, and rise to a higher level despite the fact that no measurable increase occurs in the initial tension (at x), just previous to contraction. The aortic pressure pulses (upper curves) have a larger amplitude, which at constant diastolic pressure suggests a greater systolic discharge. The period of ejection,

included between the vertical lines, is reduced. All of these features indicate a stimulating action of anoxia which is not dissimilar to that of minute doses of epinephrine.

In evaluating effects of anoxia on cardiac output by cardiometric registration it is essential that heart rate and arterial diastolic and venous pressure

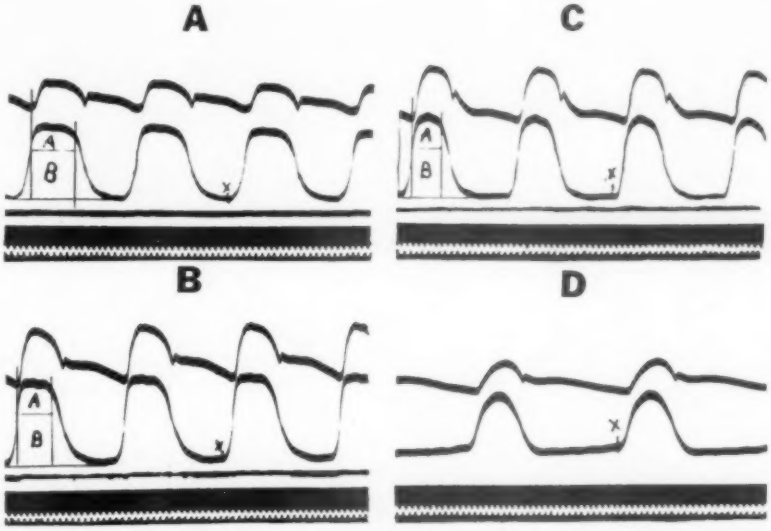

FIG. 2. Four segments of records showing changes in aortic (upper) and ventricular (lower) pressure pulses. *A*, normal, *B* at 10 per cent oxygen, *C* at 8 per cent oxygen, and *D* at 6.5 per cent oxygen in respired gas mixtures—from controlled circulation experiment. *X* indicates initial tension; vertical lines, duration of ejection; and ratio of area *A* to *B*, economy of effort.

be kept constant, otherwise secondary actions becloud the interpretations (Wiggers and Katz [17]). Furthermore, meticulous attention must be given to maintenance of an accurate placement of the cardiometer, which is often difficult to do over long periods, such as are involved in progressive anoxia experiments. I have, therefore, studied the acute effects when dogs were artificially ventilated with gas mixtures containing 6 per cent oxygen in nitrogen. In such tests cardiometer records are apt to be more reliable, for the effects begin within one minute and the whole test is completed in five minutes or less. As illustrated by figure 3, the diastolic size and the stroke volume increase within a minute or two, and continue to do so for several minutes before they are less than normal. Similar effects on cardiac output were reported by Tinsley Harrison and associates [18] and by Gollwitzer-Meier [19] who employed the Fick principle.

The most convincing demonstration that anoxia initially increases systolic discharge were those of Strughold [20] who used "controlled circulation" dogs. This investigator made moving pictures of a properly supported and oriented heart during different stages of hypoxia and anoxia. Following each experiment, every frame of the picture film was projected, enlarged, and re-

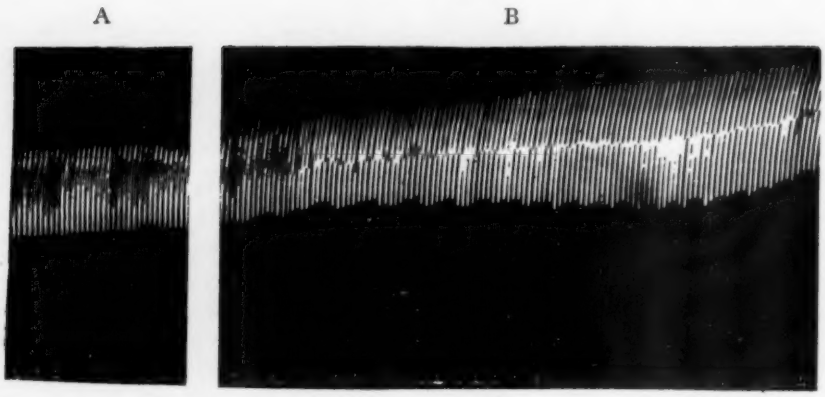

FIG. 3. Volume curves of ventricle, upstroke in diastole (*D*), downstroke during systole (S) *D–S* equals stroke volume. *A*, normal control; *B*, 48 sec. after rebreathing 6 per cent oxygen in nitrogen.

drawn, and the surface areas of the ventricles were measured at .03 second intervals. In this way, a plot of systolic ejection and diastolic filling was obtained which resembled a volume curve recorded on rapidly moving paper. During hypoxia no significant changes occurred. However, as shown by the two illustrations of figure 4, a significant increase in diastolic size and

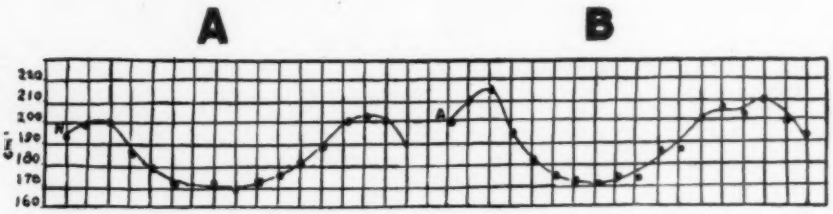

FIG. 4. Volume curves of ventricle, *A*, normal; *B*, after rebreathing 10 per cent oxygen in N (after Strughold).

stroke volume occurred during anoxia (i.e., rebreathing of 10 per cent oxygen.) Since this increase in diastolic size occurred without change in venous pressure, the inference was drawn that perhaps dilation is due to a decrease in myocardial tonus, and that such lengthening of fibers has a beneficial action on the stroke in accordance with Starling's Law.

While the ventricles are thus stimulated, they eject their blood with a greater economy of effort, as judged by a criterion suggested by Katz and myself.[21] The basis of this criterion may be explained by use of an easily understood comparison: An individual who throws the contents of a pail with some force over a high wall must expend an initial energy in raising the pail above the level of the wall and in holding it at that height, *plus* the energy required to throw its contents over the wall. The first represents *static* and the latter *dynamic energy*. The ratio of the two can be used as an expression of the economy of effort with which the act is executed. Similarly,

the left ventricle expends energy in the static effort of elevating pressure to the aortic diastolic level and of maintaining such a level during ejection. The pressure energy developed over and above this during ejection represents the dynamic effort, for it is immediately utilized to overcome resistance to systolic flow and is converted to kinetic energy of flow during the next diastole. Katz and I [21] therefore suggested that if, as in figure 2, a ventricular pressure curve is divided into areas *A* and *B*, and these areas are measured, the ratio, area *A*/area *B*, gives an index of the economy of ventricular effort. A glance at the three curves (*A, B, C*) shows that area *A* becomes somewhat larger with respect to *B* as anoxia increases. Recently, Wright, Hallaran and I [22] suggested that the method can be applied to man by recording a reliable subclavian pulse optically and determining the brachial systolic and diastolic pressures at the time. Using this procedure, Ford, Petersilge, Young and I [23] studied the economy of effort index of the human heart during progressive anoxia produced by rebreathing diminishing oxygen volumes. For this purpose, medical students rebreathed CO_2-free air from a segment respirometer of 60 liters capacity. The subject was seated and rested for 30 minutes. After connection with the mouthpiece and while breathing room air in this way, a subclavian pulse was recorded by Frank capsules and brachial pressures were determined. Heart rate could be calculated from records. The subject was then connected to the respirometer in which the percentage of oxygen decreased progressively to 14 per cent in about 5 minutes. At this point, the rebreathing mixture was kept constant by slow admission of oxygen while another set of pulse curves and brachial pressures was recorded. In a similar way, the oxygen was reduced to and stabilized at 12 and 10 per cent respectively; recordings of pulses and blood pressure being again taken. In 20 out of 23 students, in whom reliable records and data for analysis were obtained, a slight increase in efficiency was found when 14 per cent oxygen was rebreathed and a more definite increase while they were rebreathing 12 per cent oxygen. Twelve showed a further increase when the oxygen was reduced to 10 per cent; the other 8 showed some tendency for the index to decrease, but it was still above the initial values. The results indicate that anoxia exerts a stimulating action on the heart in most normal subjects and, aided by lowering of diastolic pressure, the economy with which mechanical energy is utilized is enhanced. The possibility exists that the tendency for the economy of effort to increase or decrease when 10 per cent oxygen is rebreathed may prove valuable as an adjunct to present tests for separating individuals who do and do not tolerate low atmospheric pressures.

This beneficial effect of oxygen deficiency upon the ventricle is replaced by a depressing action as the degree of anoxia becomes extreme. As a rule, this occurs when the decrease in oxygen of the respired air has exceeded 8 or 6 per cent, i.e., corresponding to a reduction of arterial oxygen saturation to 55 or 35 per cent. When this stage is reached a circulatory crisis super-

venes. As shown in the graph of figure 1, arterial pressures fall rapidly, pulse pressure is reduced, the ventricles dilate enormously, systolic discharge decreases and venous pressures rise tremendously. Similar results are reported by Gollwitzer-Meier.[19] As shown in record D of figure 2, despite a great increase in the initial tension (x), the contraction rapidly becomes less vigorous. No evidence exists that failure of the peripheral circulation occurs previous to this time, as claimed by many investigators. *The circulatory crisis is essentially an acute congestive failure of the ventricles due to the extreme anoxia.* Slowing of the heart through central vagal action and many interesting disturbances of conduction and impulse initiation take place. These have been comprehensively analyzed by Greene and Gilbert.[24] Dynamically, these disturbances serve to reduce arterial pressures still further.

The consecutive stimulating and depressing effects of anoxia on the myocardium can be demonstrated convincingly in still another manner. Tennant and I,[25] by recording the contractions of a small region of the ventricle optically, showed that the area fails to shorten within one minute after the coronary branch to that area is occluded. In such experiments the sequence of hypoxia → anoxia occurs within 100 to 125 heart beats. A review of these curves shows a fact which escaped our attention at the time, viz., that during the first 30 to 40 beats following occlusion the myographic contractions are greater. Thereafter, they become smaller and, finally, fail entirely.

The Coronary Flow During Anoxia

When the oxygen in the inspired air is reduced to 8 or 9 per cent, the volume of coronary flow increases tremendously. This was suggested by the increased flow of blood from the coronary sinus noted by Hilton and Eichholtz[26] and has recently been proved by H. Green and Wegria[27] in this laboratory. These investigators recorded not merely an increase in flow in a coronary ramus but showed by analysis of phasic flow curves that this is due predominantly to dilatation of intramural coronary branches. The pronounced anoxic vasodilation is doubtless a providential mechanism by which the cardiac pump is sustained so well in progressive anoxia; indeed, it is probable that myocardial stimulation is converted into myocardial depression as soon as the augmentation of coronary blood flow cannot keep pace with the decreasing volumes of oxygen carried by the blood.

The thought arises that the great variation in the sensitivity of different individuals to extreme anoxia and their capacity for acclimatization may depend to a large extent upon the compensatory increase in coronary blood flow which is possible. Failure of such compensatory dilatation, due to functional or morphological alterations in the main coronary vessels, may explain the poor cardiac reactions which patients with valvular or myocardial disease experience even at moderate altitudes. It may be anticipated that, when the main coronary branches are sclerotic and narrow, compensatory vasodilation of intramural vessels cannot achieve the same effective improve-

ment of circulation which occurs in the normal heart and that, therefore, such patients assume some risk even in commercial airplane transportation. Autopsy records and experimental studies [28] are in accord, however, in demonstrating that, as narrowing of the main vessels gradually takes place, collateral circulations are established from which areas involved may conceivably derive an increased blood flow, during the course of such anoxia. Until more definite evidence is available we should perhaps not be too dogmatic in interdicting air travel to individuals with evident coronary sclerosis.

In concluding this paper, may I add that it is not my purpose to minimize the effects of oxygen deficiency on reflexes and central nervous mechanisms which modulate the action of the heart and control the peripheral vessels. Nor do I suggest that many circulatory reactions of anoxia experienced in man may not involve such nervous actions. It is important, however, that in our zeal to unravel the adjustments of the heart and circulation to anoxia through moderator reflexes and central nervous actions we do not forget the equally important effects which oxygen lack has *directly* on the myocardium and coronary vessels.

Summary

In acute progressive anoxia the supply of oxygen to cells is not solely conditioned by the degree of pulmonary ventilation and the oxygen-carrying capacity of the blood; it involves also an increased blood flow.

The circulatory reactions characteristic for man, breathing gas mixtures with decreasing oxygen volumes ($20 > 6$ per cent), can be duplicated in lightly anesthetized dogs. Such experiments have the advantage that the mechanisms by which cardiac adaptations operate to increase blood flow, can be analyzed more thoroughly than in man.

During hypoxia, corresponding to progressive decrease in respired oxygen volumes to about 12 per cent, to blood oxygen saturations above 75 per cent or altitudes of 15,000 feet, blood flow is increased (*a*) regionally, by reciprocal constriction and dilatation of vessels causing redistribution of blood flow, and (*b*) generally by acceleration of the heart. The latter is due to decreased vagal tone, increased accelerator nerve activity and perhaps some direct effect on the S–A node. Stroke volume is not affected otherwise than during any cardiac acceleration. The vigor of ventricular contractions increases and the period of systolic expulsion shortens. Vasomotor changes probably occur, but there is no dynamic evidence that they are reflected in the changing systolic and diastolic pressures. Effective venous pressures fall slightly, not through reduced venous return but owing to greater minute output by the faster heart.

During true anoxia, which begins when oxygen of the inspired air is progressively decreased below 12 per cent, the heart responds with greater stroke volumes and with further increase in velocity of ejection. The economy of effort is enhanced. Experiments on dogs with "controlled circulation," i.e., in animals whose heart rate, arterial diastolic and venous

pressure, as well as alveolar CO_2 are kept constant, have demonstrated that the increased systolic discharge is accompanied by increase in diastolic size, independently of changes in venous pressure. Such compensatory reactions could probably not occur without the unquestioned dilatation of coronary vessels.

Further decline of oxygen in the inspired air to 7 or 6 per cent, corresponding to arterial oxygen saturations between 50–35 per cent and to altitudes up to 30,000 ft., leads to a circulatory crisis. Arterial pressures decline abruptly, pulse pressure is reduced, systolic discharge decreases, venous pressure rises tremendously, and various types of conduction and rhythm disturbances may occur. No evidence exists that peripheral vasomotor failure is concerned. The circulatory crisis is essentially an acute congestive heart failure due to depressant effect of anoxia on the myocardium. It probably supervenes when the increasing coronary flow can no longer keep pace with the rapidly diminishing tension of oxygen in the blood.

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HYSTERIA—SOME COMMON MISCONCEPTIONS*

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GREAT strides have been made in recent years toward dissemination of psychiatric knowledge so that there now exists within the medical profession a generally wholesome attitude toward psychiatric illnesses. This is particularly true of the psychoses. There still exist, however, attitudes on the part of many members of the profession toward certain psychiatric problems which need dispelling. The attitude toward "hysteria" seems to be the worst. It is not at all unusual to see a physician, who has previously displayed an active interest in an illness and the utmost courtesy to the patient suffering therefrom, alter his attitude completely upon receiving a diagnosis of "hysteria" from the consulting neurologist or psychiatrist. The patient usually quite rapidly senses the change and comes to feel that the physician's attitude is one of disgust or pity rather than of interest and sympathy. Therapy under such conditions is doomed to failure.

It is the purpose of this paper to attempt to clarify certain erroneous conceptions regarding "hysteria" which seem to have played a major rôle in fostering these unwholesome attitudes. It is noteworthy that many, perhaps the majority, of practicing physicians include under "hysteria" all the psychoneuroses.

The psychiatric knowledge possessed by the general medical practitioner must of necessity be conditioned by reading psychiatric textbooks rather than by experience. It is, therefore, the textbooks which must be searched first for possible clues to explain these existing misconceptions. It is here that we make our first astounding discovery. The description of "hysteria" and the elaboration of the personality traits of the patient suffering therefrom contained within most of the present-day textbooks are not applicable to the majority of the "hysterical" illnesses or symptoms which are seen by the psychiatrist today. There are reasons for this.

In the past our knowledge of psychiatric illnesses has been achieved for the most part by the study of patients who were delivered in toto to the psychiatrist and usually into the confines of a psychiatric institution, frequently even a state hospital. This is the knowledge recorded in most psychiatric textbooks.

Much of the newer, present-day psychiatric knowledge is being obtained by physicians who practice extramural psychiatry or psychiatry in a general hospital.[1] These physicians are seeing illnesses or ofttimes only isolated symptoms which are obviously "hysterical" or "functional" or "psychologically determined," depending upon which terminology you prefer; yet in very few respects do these illnesses or the patient suffering from them fit

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the concepts of the labeled illnesses of present-day psychiatric textbooks.

In fact, it seems quite likely that following the present intensification of psychiatric education in medical schools wherein a part of the examination of almost every patient studied in the teaching centers is a psychiatric evaluation of his illness, many present-day concepts of psychiatric illnesses will be considerably altered.

There are two very common misconceptions regarding "hysteria" which are closely allied and can be discussed together. First, that "hysterical" symptoms or illnesses are more or less identical with malingering, intimating thereby that the patient is just putting them on. In one book, perhaps unwittingly, the author has listed under "Tests for Malingering" the ways of differentiating "hysterical" from "organic" symptoms and signs.[2] Second, that no symptom is "hysterical" unless it can be mimicked volitionally.[6, 8]

In discussion it may be pointed out that except in those rare cases of so-called "professional malingering," wherein there is direct monetary gain to be had by faking a non-existent injury, true malingering in psychiatry is for all practical purposes non-existent. Instead of being looked upon as purely volitional, "hysterical" symptoms should be regarded as evidence of illness in the broad sense of the term. The multitude of intricacies entering into the formation of an "hysterical" illness and those various perplexing factors which determine the formation of specific symptoms, whether they be "situational," "physical" or "psychical," are of such complexity that they can rarely ever be either easily or completely understood. The point to be emphasized is that such illnesses should not be denied merely because it is difficult or impossible to completely understand them. Careful and detailed studies by a number of men of various schools of psychiatric thought have scientifically established the illness factor in these cases. It is wise for the physician not thoroughly grounded in psychiatry to just accept this without asking for specific proof in the individual case.

The misconception that nothing is "hysterical" unless it can be mimicked volitionally probably has its roots in the fact that this is often true for the striped muscular phenomena. However, it does not hold true for either the sensory or the visceral manifestations of the illness. It is generally stated concomitantly with the above that the "hysterical" symptom is one which may be reproduced under hypnosis.[7] This seems to have fixed more strongly in mind the concept that the "hysterical" symptom is, therefore, volitional. In explanation it may be pointed out that there is considerable difference between an individual's ability to perform some act strictly volitionally and his ability to perform the same act while under hypnosis. In addition, almost every psychiatrist has seen "hysterical" symptoms which have not been reproduced under hypnosis.

For the successful treatment of "hysterical" symptoms it sometimes seems wiser to consider them as "organic" nervous system lesions. If the physician assumes this sort of attitude toward the lesion and the patient

suffering therefrom and at the same time is cognizant of the fact that this particular "organic" lesion is the result of disturbances which are mainly "psychologic" and can usually be cured by therapy which is predominantly "psychologic," both the patient and the physician will be much better satisfied with their contacts with each other.

Many physicians feel that the "hysterical" patient is not trying to get over his symptoms or his illness and that if he would only try, he could be well. The blame for this misconception lies on the shoulders of the psychiatrists who have made so popular the misleading terms "flight from reality" and "escape into illness." [3, 10]

The occasional reader of psychiatry gains the impression when studying the exponents of this misconception that "hysterical" patients quite eagerly and with perfect awareness of what is transpiring avoid unpleasant situations by embarking on this perfectly enjoyable thing called "hysteria." Such is certainly not the case. Patients experiencing an "hysterical" illness, if it is at all severe, almost invariably endure marked suffering at one time or another during the course of the illness. Even those "hysterical" cases who display an outward appearance of indifference to rather disabling symptoms usually suffer considerable discomfort as their symptoms change during the course of therapy.

Instead of looking upon the "hysterical" patient as having "escaped into illness," it is wiser to regard the "hysterical" illness or symptom in one of two ways. Regard it as being the temporary result of an honest effort on the part of the patient to solve a difficult problem. In so trying to solve a difficult problem, the patient's efforts may have been misdirected and the "hysterical" symptoms be the result. But he has really tried to solve the problem. He has not consciously tried to "escape." Another way of looking upon the "hysterical" patient or the "hysterical" symptom is to regard it as being the result of a large number of varied factors (all the way from the constituents of the circulating blood to the excitations set in play by incoming visual stimuli) acting upon the nervous system. Some of these factors may be altered or the intensity of the excitations may be lessened so that a different reaction will ensue. Either of these ways of thinking will stimulate scientific inquiry into the causative factors and point the way toward a more healthy solution or reaction.

The misconception that "hysterical" patients never do anything which results in injury to themselves or else only very minor injury [7] causes unnecessary accidents. In fact, when a "fit" is suspected of being "hysterical," it is not unusual for the physician to recommend that no attempt be made to catch the patient should he roll from the bed because it is said that the "hysterical" patient will see to it that he is not injured.

This is a good therapeutic practice with some patients but a dangerous one with others and is a decision best left to the specialist. Although there exist cases displaying "hysterical" episodes only when an audience is in attendance, not all "hysterical" episodes are so occasioned.

Despite the laudable effort many physicians are making today to sharply define and separate "epilepsy" and "hysteria,"[11] the accomplishment of this in many cases is difficult unless one takes the stand that the diagnosis of "epilepsy" rests upon the demonstration of the characteristic electro-encephalographic cerebral dysrhythmia. It is not fashionable in this day to speak of "hystero-epilepsy," yet the physician should remember that there are cases presenting the syndrome of episodic loss of consciousness with accompanying "fits" but who lack the electro-encephalographic abnormalities seen in "epilepsy" and whose "fits" are often controllable by psychotherapy. They injure themselves or occasionally others in about the same way and about as frequently as "epileptics" do.

There is another group of "hysterical" illnesses, sometimes labeled "dissociation hysteria," in which the patient suffers actual clouding of consciousness with all its attendant dangers and during which he must be protected in the same way that one would protect an acute schizophrenic. While speaking of the injury danger in "hysterical" patients, we should remember that suicide in such cases is not unknown. Attention is called to the statistics on suicide[12] where it is noted that a relatively small percentage of the patients were thought to be psychotic. What then should be the diagnosis pinned to the larger percentage?

Of all the misconceptions regarding "hysteria" the one which most frequently engenders an unwholesome attitude toward the patient and which inclines the physician toward therapeutic nihilism is the belief that every individual suffering from "hysteria" has a specific constitutional inadequacy which predisposes to the development of this particular type of illness.[4, 9, 13, 14] There is even much written about a specific "hysterical personality." The psychiatric study of all cases coming for medical aid, even for obvious "physical" illnesses, has revealed facts at variance with this misconception.

While it is common knowledge that some individuals react to nearly every unpleasant stimulus with an "hysterical" episode, it is not so generally realized that under the proper conditions, the exact nature of such conditions varying somewhat depending upon the individual in question, any individual—no matter how well born or how well integrated—can be made to display what we today call "hysterical" symptoms. If there is to be described a specific constitutional defect which predisposes to the development of "hysterical" symptoms, then such a description must be used to describe the entire human race and not just a portion thereof.

The difficulty is in deciding what differentiates a few "hysterical" symptoms from "hysteria." A widely read book hints at this when at the start of the chapter on "hysteria" the reader is cautioned against mistaking "hysterics" for "hysteria."[5] Yet it fails to make clear where one must draw the line. It is to be hoped that some author will attempt a solution of this problem. At the present a generally satisfactory solution does not exist. "Hysteria" today includes within it a numerous and varied set of

related conditions about which the final word has not been written. It is known that there may be all degrees of severity of "hysterical" illnesses just as there may be all degrees of severity of "physical" illnesses.

For proof of the above the following two points are offered to stimulate observation, although innumerable ones could be listed. The psychiatric study of patients who seek medical aid because of obvious "physical" ailments reveals that even many of these patients consistently present signs and symptoms which could not be produced by the isolated pathological lesion but which represent instead the influence of that lesion upon the individual's nervous system (including "psyche") effecting a "functional" or "hysterical" symptom. Such symptoms frequently subside simultaneously with the physician's diagnosis and reassurance of recovery before the pathological lesion has changed one whit.

Those who have had the opportunity to be consulted by medical students have ample proof of this misconception. Medical students are selected from a large group of applicants because of their superior intellectual ability, their excellent hereditary background, their constitutional soundness and a previous record indicating a fine state of integration of their faculties. Yet, at some time during the course of their medical school existence with all its newness, its mysteries, the threats of failure and the excessive demands which such a study-course makes upon one, no small number of these students display either isolated symptoms or else full-blown illnesses which are obviously and frankly "hysterical," usually more politely labeled "functional." Despite suffering these temporary "hysterical" symptoms or illnesses, these same students usually go on to complete recovery and in the future a fine state of mental health as practicing physicians. As well-integrated practicing physicians occupying a respected position in their communities, no one ever looks upon them as having an "hysterical" personality or a specific constitutional defect. Yet these same men have suffered many "hysterical" symptoms.

Summary

It has been pointed out that there still exists within the medical profession a rather unwholesome attitude toward "hysteria" and the patients suffering therefrom. A few of the outstanding misconceptions regarding "hysteria" which tend to promote such an attitude have been discussed. They are in order:

1. That "hysterical" symptoms or illnesses are more or less identical with malingering, intimating thereby that the patient is just putting them on.
2. That no symptom is "hysterical" unless it can be mimicked volitionally.
3. That the "hysterical" patient is not trying to get over his illness and that if he would only try, he could be well.

4. That "hysterical" patients never do anything which results in injury to themselves or else only very minor injury.

5. That patients suffering from "hysteria" have a specific constitutional defect which predisposes to the development of this illness.

A case contradicting almost all of these common misconceptions is presented in brief.

Case Report. J. L., aged 57, was admitted to the hospital with the complaints of blindness, paralysis and pains in the back and legs. Family history showed only that the father and mother lived to advanced ages and that the patient was one of nine farm-raised siblings. Past health had been excellent. The patient had been married 38 years and had six living children. Patient had made a satisfactory living as both farmer and night watchman in a sawmill, and was considered by his friends and family as having been a well-adjusted and stable individual prior to his present illness. The present illness had begun seven years prior to entry with the gradual onset of pains of intermittent nature in his lower extremities. These pains were not severe enough to keep the patient from working. Eighteen months prior to entry patient had the onset of a period of disturbed consciousness lasting about five minutes and followed by markedly diminished vision and dizziness. During the next several weeks spent in bed he developed various tremors of face, hands and legs. After several weeks his vision partially returned and he was able to walk about the house with aid. During the next several months he had repeated attacks, each similar to the first. The last attack occurred six months before admission, since which time he had not been able to distinguish between light and dark. The tremors increased in severity, particularly about the face and upper extremities. For the most part he had been bedfast, at times unable to move his lower limbs at all, due to increasing stiffness.

Physical examination showed a malnourished, middle-aged white man with evidence of marked weight loss and moderate dehydration. There was purulent exudate from the ocular conjunctivae. The eyelids were in a constant state of motion, alternately opening and closing, while the eyeballs also constantly moved slightly in an upward and downward motion but could not be moved to either side. Pupils responded to light but light perception was absent. The disks were quite difficult to visualize; they appeared somewhat pale but well outlined. There was marked dental caries, and the tongue was dry and coated. There was moderate generalized arteriosclerosis with normal blood pressure. The heart, chest, and abdomen revealed nothing remarkable. Neurological examination showed marked spasticity and marked weakness of all extremities, most marked in the legs, with evidence of moderate muscular wasting. Attempts to passively move the legs elicited complaints of pain. There was generalized hypoesthesia over the entire body with anesthesia below the hips. The Romberg was positive with patient falling always to the left. There were typical striatal tremors of the hands and head, with fibrillary twitchings occurring over the face and occasionally observed in the arms. Of the reflexes the gag and corneal were both active, the biceps and triceps were active and equal, the knee jerks were bilaterally hyperactive, while neither abdominal nor ankle jerks could be obtained. The blood Wassermann test was negative; the red blood count was 4,800,000, the white count 6,320 with a normal differential. The spinal fluid showed initial pressure of 140 mm. of water with only one cell and normal Queckenstedt test. Spinal fluid Wassermann test was negative, as was the colloidal mastic. Roentgen-rays of the teeth showed extensive alveolar absorption. Roentgen-rays of the spine showed an extensive hypertrophic arthritis. An electro-encephalogram showed normal alpha rhythm.

The first week was spent in improving the patient's state of nutrition by forced feedings, intravenous fluids, extra vitamins, etc. The conjunctival infection was

cured, the decayed teeth were removed and a normal state of hydration was achieved. However, the patient remained blind, being unable to distinguish light from dark although the pupils reacted. Rotation of a lettered drum before his eyes failed to induce nystagmus. The motor and sensory changes persisted.

Intensive psychiatric therapy was started with daily interviews which included efforts to determine the causative factors, positive suggestive therapy, sub-convulsive dosages of metrazol given intravenously, etc. The patient rather rapidly improved on this therapy. His sight gradually returned, he became able to walk, the spasticity disappeared, the anesthesia disappeared and finally even the tremors disappeared. The disturbing situational factors were adjusted satisfactorily by conferences with the patient's family, and the patient returned to his home. He has remained well during the eight months he has been at home.

This case is enlightening. When first admitted, the more the patient attempted to control his disturbing symptoms by volitional effort—and he made honest efforts to do so on command—the worse these symptoms became. None of the many physicians who saw this patient could mimic the twitchings, the spasticity in flexion or the anesthesia which he presented. It might be argued that since he was cured by psychotherapy, the twitchings observed could not have been fibrillary. This, of course, is true, but it is not important. Several experienced neurologists examined this patient prior to efforts at psychotherapy, and agreed that the twitchings were fibrillary in nature. The usual tests for distinguishing an "hysterical" from an "organic" illness, such as the rotation of a lettered drum before the eyes to induce nystagmus, the Hoover's sign, etc., all pointed to an "organic" rather than an "hysterical" illness. There was argument among the physicians as to diagnosis which was only settled by the cure by psychotherapeutic methods. The patient had been a well-integrated individual without previous evidence of "hysterical" personality for 50 years prior to the development of this illness. No evidence of constitutional inadequacy could be found—unless one includes such factors as arteriosclerosis and arthritis as evidence of constitutional inadequacy. The illness was of such severe nature that it had resulted in muscular wasting, secondary infection and malnutrition, all increasing in severity so that had not some intensive therapy been undertaken, it seems quite likely that the patient might soon have died.

The psychopathologic factors included lowered capacity to adjust, due to arteriosclerosis and advancing age, the disturbing and incapacitating pain of arthritis, while the illness was precipitated by certain disturbing situational factors. No attempt has been made to discuss them completely or to elaborate on the finer details of the psychotherapeutic measures employed. It is only noted that they were present, they were altered by psychotherapeutic methods, including the chemotherapy of metrazol injections, and the patient was cured of his "hysterical" illness and was taught to live with his "physical" illness.

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CASE REPORTS

IDIOPATHIC HYPOPARATHYROIDISM; A REPORT OF 2 CASES *

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HYPOPARATHYROIDISM is a condition which the internist meets fairly commonly. It generally results from the inadvertent removal of one or more parathyroid glands in the process of thyroid operations, more rarely after the purposeful removal of one or more adenomatous or hyperplastic parathyroid glands to alleviate hyperparathyroidism.

The metabolic and chemical abnormalities of hypoparathyroidism were clearly defined by Albright and Ellsworth in 1929.[1] Since that time much has been added to our knowledge of the therapy for this condition; and an especially valuable recent addition to our therapeutic armamentarium is dihydrotachysterol (A. T. 10).[2, 3, 4, 5, 18]

Very rarely one sees patients with hypoparathyroidism who have undergone no surgical procedures in the cervical region, and in whom the etiology of the parathyroid insufficiency is completely unknown. The group at the Massachusetts General Hospital[6] has recently reviewed the literature on this condition and added six cases of their own. We were fortunate during the past year in having under our observation simultaneously two patients suffering from hypoparathyroidism of unknown etiology. The findings in both patients fulfilled all the criteria for this diagnosis as laid down by Albright and Ellsworth.[1] Each patient presented certain quite unusual features, and, in view of the great rarity of the condition, we have felt that a report of our observations was justified.

CASE 1

J. H., a 15-year-old school-boy, was first brought to the Harriet Lane Infirmary, of the Johns Hopkins Hospital in January, 1928 because of photophobia and excessive lacrimation. He was then 4 years old. His parents had noted that, ever since an attack of measles followed by whooping cough at the age of two years, light hurt the child's eyes, and that he protected them either by keeping them shut or by holding something over them.

Examination at that time showed a normally developed child. He persisted in keeping his eyes closed or covered. There was marked lacrimation, and when a glimpse of the conjunctivae could be obtained "small points of epithelial defects" were seen. A diagnosis of phlyctenular kerato-conjunctivitis was made. In addition it was noted that the hair on the head was thin and patchy, and that his eye-brows and lashes were sparse. The skin was dry, the teeth discolored and irregularly developed, the nails short and thickened. The tonsils were enlarged. In other respects the general examination was negative. The blood Wassermann reaction was negative,

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but the tuberculin test gave a positive reaction in a dilution of 1–100,000. Roentgen-ray of the chest was normal. Skin and hair changes were considered to be "multiple congenital ectodermal defects."

A tonsillectomy was performed, and during the next two years the patient was given tuberculin therapy, ultra-violet irradiation, and cod liver oil. There was complete disappearance of the kerato-conjunctivitis but no change in the photophobia or blepharospasm.

The patient was not seen again until December, 1937, when he was referred to the Wilmer Clinic by the school doctor because of persistence of the photophobia. In the interim he had been perfectly well in every other respect, participating normally in school activities and maintaining an average grade in his studies. Because of a suspected endocrine disorder, the patient was referred to the Medical Clinic. Toward the end of the physical examination the patient happened to bump into the examiner and his facial muscles were seen to twitch. Chvostek's and Trousseau's signs were then sought, and both were found to be positive. In another laboratory serum calcium was found to be 6.2 mg. per cent.

The patient's family history is entirely non-contributory. His mother and father are living and well as are also six siblings. There is no familial history of tuberculosis.

The patient's birth and development up to the age of 2 years were apparently perfectly normal. He had had chicken pox at the age of 18 months, measles and whooping cough at 2 years, as previously mentioned, and mumps when he was 2½ years old. Aside from the eye trouble and infrequent upper respiratory infections, his general health had been excellent. At no time had he ever had convulsions or complained of muscular cramps or paresthesias. Sweating had always been normal. There had never been any cough, stridor, or other respiratory symptoms. No history of gastrointestinal or urinary symptoms was obtained. In 1937 he fractured his right humerus playing base-ball, but this was the only history of any bone injury. The fracture healed normally.

Because of lack of coöperation on the part of the family, the patient was not seen again for nine months.

On September 27, 1938, he was persuaded to come to the Johns Hopkins Hospital for study. The abnormal physical findings at this time were confined chiefly to ectodermal structures. The skin was dry, coarse, and scaly. The hair was very thin and patchy on the head and absent in the axillary and pubic regions. The head was unusually long with prominent occipital and frontal bosses. The eye-lashes and eyebrows were scanty.

The appearance of the external surface of the lids may be seen in figure 1. Examination of the eyes was difficult because the lids closed spasmodically when attempts were made to examine them. A liberal dose of sedative and instillations of pontocain solution somewhat facilitated examination. There were no lesions on the palpebral or ocular conjunctivae or on the corneae, and consequently there was no apparent reason for the blepharospasm. Visual acuity was 20/20 O.U. The ocular fundi seemed normal and ophthalmoscopic examination failed to reveal opacities in the media. Slit-lamp examination revealed only lenticular changes. Small, white, irregularly-shaped opacities—for the most part subcapsular but also present in the outer cortex—were seen both anteriorly and posteriorly.

The teeth showed marked deficiency of enamel formation with delayed and irregular eruption of the deciduous teeth and retarded development of the permanent teeth (figure 2). The finger and toe nails were short, thick, and largely overgrown by skin (figure 3). There was a strongly positive Chvostek's sign, and Trousseau's sign was positive after the tourniquet had been applied 90 seconds. No other abnormalities were noted in the physical examination. The height was 155.6 cm., the span 154.6 cm., and his weight 48.2 kg. Blood pressure was 110 mm. of Hg systolic and

60 mm. diastolic. Laboratory data: Hemoglobin, red blood cells, and white blood cells were normal. Examination of the stool and urine showed no abnormalities. Non-protein nitrogen: 33 mg. per cent. Phenolsulphonphthalein excretion: 30 per cent in 15 minutes and 64 per cent in 2 hours. Urea clearance: 83 per cent normal maximum clearance. Blood Wassermann: negative. Serum calcium: 5.0 mg. per cent. Serum inorganic phosphate: 12.1 mg. per cent. Total serum protein: 7.1 gm. per cent (refractive index method). The blood was found to have a vitamin A con-

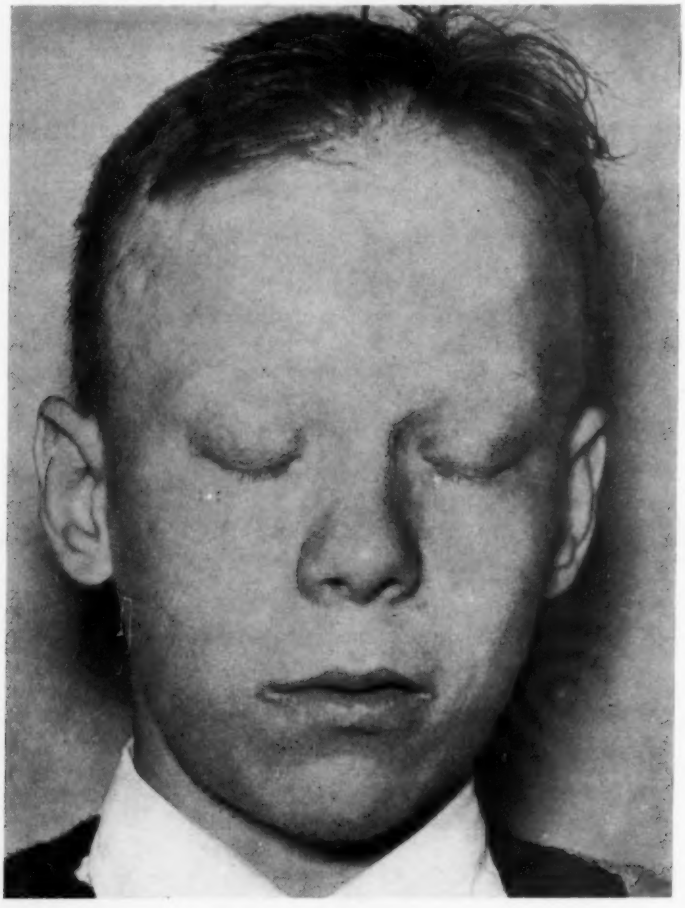

FIG. 1. Note sparsity of eye-brows and lashes and the thin, patchy scalp hair.

tent of 0.4 unit (lower limit of normal by the method is 0.7–0.8 unit). Clotting time: 18 minutes (normal: 6–12 minutes). Basal metabolic rate: plus 29 and plus 18 on two separate occasions, but the tests were not very satisfactory. The electrocardiographic record showed a levogram with low T_2 and prolonged QT interval but no other abnormalities.

Roentgen-ray reports: Heart and aorta normal. Lungs clear. Head: Normal skull. Intravenous pyelogram: Negative. Bone roentgen-rays: Bones of extremities, pelvis, and spine show increased density and sclerosis throughout (figure 4). Bone age as determined by roentgen-ray was normal.

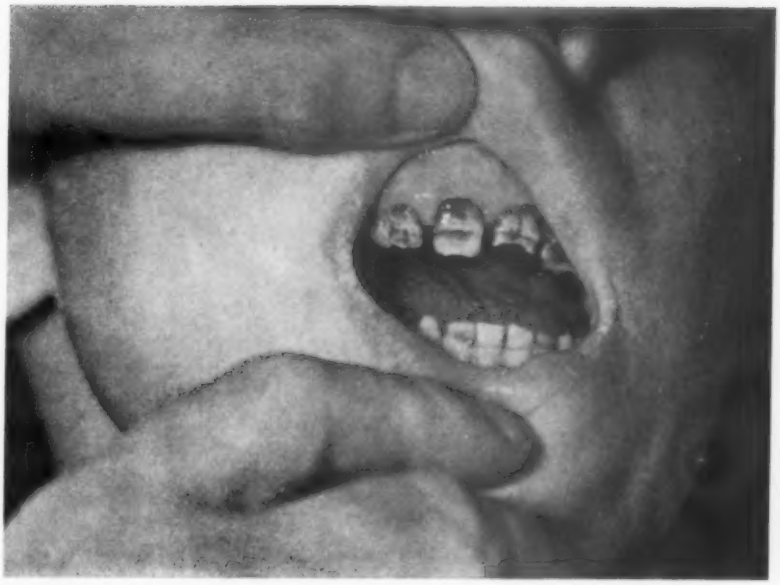

FIG. 2. Note deficiency of enamel formation of incisor teeth.

FIG. 3. Note rough, short, thick fingernails resembling somewhat the appearance in epidermophytosis.

Samples of the patient's fingernails were found to have a cystine content of 7.12 per cent by Dr. Sullivan of Georgetown University. This value was considered to be significantly below the normal value of 11 to 12 per cent.

Dental reports (November, 1938): "There has been much interference with the developmental processes of the dental organs. The enamel of the incisors and 6 year

FIG. 4. Note the greatly increased calcium deposit with normal bone architecture.

molar teeth, which is developed in the first year of life, is markedly hypoplastic, while that of the bicuspids and 12 year molars (as seen by roentgen-ray) is more perfectly formed. There is gross malarrangement of the teeth of both arches, which is in all probability due to the disharmony between the exfoliation of the deciduous teeth and eruption of the permanent. This condition has proceeded to such an extent that several of the permanent are definitely impacted in bone and will either never erupt or will erupt far out of their normal position." (Figures 2 and 5.)

SPECIAL STUDIES

Chart 1 shows the results of the calcium and phosphate balance studies carried out. The periods are consecutive and each one represents the daily average of stool and urine analyses for five days. During the first period the patient was on a diet low in calcium and moderately high in phosphorus. He was barely able to maintain a positive calcium balance but showed a definite phosphorus re-

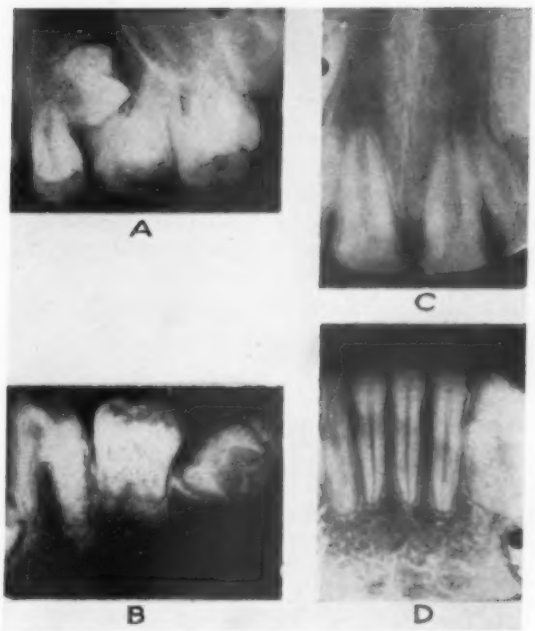

FIG. 5. *A* and *B*. Molar teeth. Note retardation of development and eruption as well as increased density. *C* and *D*. Incisor teeth. Note hypoplastic enamel at incisor edge and general lack of development as well as the increased density of the remainder of the tooth and also increased density of the mandible as evidenced by the increased prominence of the bony trabeculae.

CHART I

Calcium and phosphorus balance in case 1 on low calcium, normal phosphorus diet; high calcium, low phosphorus diet and with dihydrotachysterol therapy.

5 Day Periods	Calcium				Phosphorus				Serum		Therapy
	Urine gm. per day	Feces gm. per day	Intake gm. per day	Balance gm. per day	Urine gm. per day	Feces gm. per day	Intake gm. per day	Balance gm. per day	Ca mg. %	P mg. %	
1	.030	.088	.137	+.019	.422	.104	.741	+.215	5.2 (I)	13.3* (I)	
2	.029	.618	1.697	+.868	.192	.351	.349	−.194	5.3 (I)	12.5 (I)	
3	.029	1.256	1.697	+.230	.133	.223	.349	−.007	6.1 (V)	9.6 (V)	
4	.049	.846	1.697	+.620	.056	.259	.349	+.034	7.9 (V)	9.6 (V)	A.T. 10 3 c.c. for 3 days 1 c.c. for 2 days

* The Roman numerals indicate day of period on which blood sample was taken.

tention. In the second and subsequent period the diet was changed to one of high calcium (12 gm. added calcium lactate) and low phosphorus. The sharp rise in the calcium balance in the first five days following the dietary change was undoubtedly due to a lag in fecal excretion and equilibrium was not attained until the third five day period. It is noteworthy that during 10 days on a high calcium low phosphorus diet without other therapy there was a significant drop in serum phosphorus and rise in serum calcium, thus tending to corroborate the findings of Anderson and Lyall [7] and Shelling,[8] and confirming the importance of a low phosphorus diet in the treatment of hypoparathyroidism.[9, 7, 14] It is probable that with the phosphorus content of the diet constant, raising the calcium intake alone will diminish the absorption of phosphorus and thus lower the serum phosphorus, as suggested by the experiments on rats of Shohl and his collaborators.[22]

During the fourth period dihydrotachysterol was administered and, as has been found by other authors,[4] there resulted a marked increase in the absorption

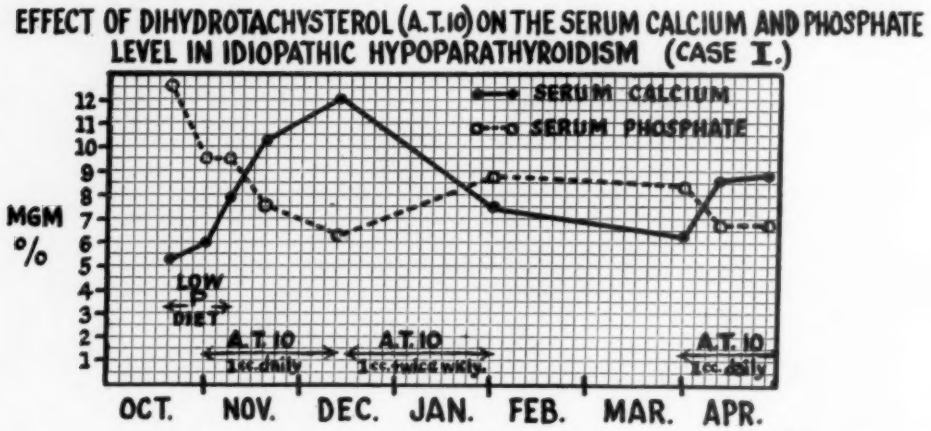

CHART 2. Showing the level of serum calcium and phosphorus and phosphatase as influenced by dihydrotachysterol therapy.

of calcium from the gastrointestinal tract with a coincidental rise in serum calcium. Contrary to the findings of others,[4] however, there was a decrease in urinary phosphate excretion with no significant change in phosphate balance or serum phosphate level. Unfortunately, we were not able to continue the balance studies for more than a single five day period on dihydrotachysterol. Hence, we cannot say whether this effect of dihydrotachysterol on the phosphate balance was only a transient one, or whether it may have been related to the relatively small quantity of drug administered, to the low intake of phosphorus or to some other factor.

Chart 2 shows the effect of more prolonged administration of dihydrotachysterol on the serum calcium and phosphate level in patient 1. It will be noted that on a daily dose of 1 c.c. the serum calcium rose to 12.2 mg. per cent at the end of six weeks, while the serum phosphate fell to 6.3 mg. per cent. A dose of 1 c.c. twice weekly, however, was not sufficient to maintain normal serum calcium and phosphate levels. During this whole time the patient received 12 gm. of calcium lactate and 10 minims of oleum percomorph daily. The intake

of phosphorus was not restricted, however, and it is of some interest that the serum phosphate remained abnormally high even when the serum calcium level had risen to normal. At no time did the patient exhibit active tetany although Chvostek's and Trousseau's signs became positive whenever the serum calcium level was sufficiently depressed. During the period shown in chart 1 there was no significant variation in the total plasma protein level. Except for the disappearance of the signs of tetany and considerable decrease in the severity of the blepharospasm there had been little demonstrable change in the patient's general condition or in the ectodermal, osseous, or ophthalmological disturbances at the termination of this study. Subsequent to hospital discharge the patient was again lost to observation for awhile. In October, 1939 a general examination showed no essential deviation from his status in the fall of 1938. The appearance of the bones in roentgenograms was unchanged, the blepharospasm persisted, and serum calcium and phosphorus were essentially the same as before therapy. He stated that he had taken dihydrotachysterol very irregularly, not more than 75 days out of the year.

Discussion of Case 1

That this patient's parathyroid glands were really underfunctioning and that there was not some sort of tissue resistance to parathormone seems proved by the vigorous response in urinary phosphorus excretion when parathormone was

Chart 3

Urinary excretion of phosphorus in case 1 before treatment, showing excretion of phosphorus in the response to 2 c.c. parathormone given intravenously. Compare control period which shows no increased phosphorus excretion after 2 c.c. normal saline intravenously.

Time	Control Period				Parathormone Test					
	Water Intake	Urine Volume c.c.	Urine P mg.	P/hr. mg.	Water Intake	Urine Volume c.c.	Urine P mg.	P/hr. mg.	Serum P mg. %	Serum C mg. %
7–8 a.m.	200	12	1.4	.023	200	58	22.3	.361		
8–9 a.m.	200	195	21.4	.357	200	112	24.5	.395		
9–10 a.m.	200	?	26.5	.434	200	218	21.6	.366	12.5	5.3
Normal saline 2 c.c. intravenously 10 a.m.					Parathormone 2 c.c. (200 units) intravenously					
10–11 a.m.	200	240	26.0	.474	200	182	82.0	1.344		
11–12 Noon	200	160	24.6	.432	200	170	109.0	1.786		
12–1 p.m.		150	25.8	.432		53	35.3	.631		
4 p.m.									11.0	6.9

given intravenously (chart 3). The procedure used in this experiment was identical with that previously used by us [10] in testing patients' sensitivity to parathormone. It can be seen from the chart that this boy's fasting urinary excretion of phosphorus was approximately that of a normal person. In our

former studies [10] it was found that in hypoparathyroid subjects the fasting urinary excretion of phosphorus was very low. We are not sure why in this case the urinary phosphorus was high, but it may have been due to the very high serum phosphate in this patient—none of our former patients having shown nearly so high a value. When parathormone was injected the urinary phosphorus excretion increased four-fold. This response is of the same order of magnitude as seen in normal persons, though of course their serum phosphate level is from 3 to 4 mg. per cent instead of 12 mg. per cent as in our patient.

At a later date the test was repeated at a time when serum phosphate was 9.2 mg. per cent. The fasting urinary excretion of phosphorus then averaged 4 mg. and increased to 60 mg. per hour after intravenous parathormone injection.

The skin, nail, and hair changes shown in this boy have been reported in other patients suffering with this disease. Just how such anomalies are brought about is unknown, but since they occur apparently in postoperative hypoparathyroidism also, they must be ultimately due to the deficiency of parathyroid hormone and not due to whatever may be the etiologic factor that destroys the function of the parathyroid gland in idiopathic hypoparathyroidism. Furthermore the cutaneous abnormalities have been reported to have disappeared entirely under appropriate therapy.[12] The teeth show the alterations in structure which have been emphasized by Albright as being characteristic of hypoparathyroidism in juvenile patients [11] and are similar to those described in parathyroidectomized young rats.[19, 20,23]

The finding of an abnormally low cystine content in the fingernails is of interest as indicating a disturbance in sulfur metabolism. Whether or not further studies along these lines may shed light on the nature of the ectodermal defects cannot be stated at the present time.

Excessive bone formation such as occurred in this boy has not, to our knowledge, previously been noted in this condition, though it is perhaps what might be expected. *Hyper*parathyroidism with its high urinary excretion of calcium and phosphorus, in the absence of an adequate calcium intake to maintain equilibrium, results in generalized rarefaction of the skeleton. *Hypo*parathyroidism, in the presence of a high calcium and phosphorus intake as was true in this case, might reasonably be expected to show bones denser than normal. Since, from the history, it seems fair to assume that deficient parathyroid function had been present in this boy since the age of two and probably since birth, one may conclude that his osteoid tissue was laid down and calcified in a medium far higher in phosphorus and lower in calcium than normal. Dr. Edwards A. Park, on seeing our patient, recalled some of his experiments on rats which had been fed low calcium and high prosphorus diets. The bones of these rats seemed structurally normal but exceedingly dense—quite like those of our patient. After seeing our patient, Dr. Fuller Albright has recently reëxamined the bones on several of his juvenile patients with idiopathic hypoparathyroidism and found the bones to be of increased density in all of them.[11]

Case 2

C. R., a 56-year-old unmarried school teacher entered the Phipps Psychiatric Clinic on May 29, 1938 because of an agitated depression. She had had two previous depressive episodes; the first in 1906 lasted only a few months, the second began in 1930. At this time, because of menorrhagia, the pelvic organs were irradiated with

subsequent cessation of the menses but with very minor vasomotor menopausal phenomena. There was no apparent effect of this artificial menopause upon the depression which deepened and lasted about 18 months with gradual recovery.

From 1932 until her present illness began she had seemed her usual self and had carried out normally her duties as school teacher. During the winter of 1937–38 she had seemed more irritable and to have less interest in her work. On April 15, 1938 an explosion occurred in a refrigerator tank at the school. Ammonia fumes escaped in large amounts. The patient remained calm despite pandemonium among the children, saw all her pupils removed from the building in orderly fashion and then left the building herself. She is said to have fainted momentarily after her own exit, but recovered promptly and went home unassisted. Observers stated that there were no convulsive or tetanic manifestations at this time.

The following day, because of feelings of great nervousness and tension dating from the time of the explosion, the patient went to a Turkish bath establishment. After a brief period in a steam cabinet she suddenly developed carpopedal spasm, contractile pains in the intercostal and abdominal muscles, and difficulty in breathing. This attack lasted about 20 minutes with gradual release of the severe spasticity. But the symptoms never entirely disappeared and returned in severe form several times again before her admission to the hospital. There was almost constant "breathing difficulty and congestion of the nasal passages" which was attributed to the irritation of the ammonia fumes.

She continued to be highly nervous and in the two weeks immediately prior to her admission there was an acute return of her depressive symptoms with frequent crying spells. On May 2 the patient's eyes were examined because she was having trouble with close work. A refractive error was found but her ophthalmologist writes: "The lenses were entirely clear."

Her past history revealed little else of interest. She had been known to have a dorsal scoliosis since childhood but never suffered with any symptoms from it. The dietary history revealed no abnormalities. She had always eaten much fruit and green vegetables, ate meat once daily, and drank on an average 400 c.c. of milk daily.

On admission to the Phipps Clinic on May 29, 1938 the patient was in a highly excitable agitated state. General physical examination revealed only the following abnormal findings: Gross tremor of the extended fingers, involuntary twitchings of the brachial and thoracic muscles, and a positive Chvostek's sign. Laboratory examinations: Hemoglobin 13.8 gm.; red blood cells 4.64 millions; white blood cells 5,000. Sedimentation rate 31 mm. Smear and differential count were normal; no eosinophilia was present. Non-protein nitrogen 36 mg. per cent; fasting blood sugar 112 mg. per cent. Wassermann reaction negative. There was a bare trace of albumin but no other abnormality in the urine examination.

Skeletal roentgen-rays were interpreted by Dr. John Pierson: "Moderate demineralization of all the bones." (Figure 6.)

On May 31, 1938, two days after admission, the record shows a serum calcium determination of 10 mg. per cent. In the light of previous and subsequent events the correctness of this calcium determination seems open to question. No inorganic phosphate or serum protein evaluations were made at this time.

Course in Hospital. The curious cyclical alterations in behavior during the early part of her hospital stay have been made the subject of a separate communication by Richter.[13] Because of the development of active tetanic manifestations in mid-August, serum calcium and phosphate determinations were made. The calcium value proved to be 5.0 mg. per cent and the phosphate 8.7 mg. per cent. Phosphatase activity 1.2 Bodansky units. The course of her serum calcium and phosphorus values and anti-tetanic therapy may be seen on chart 4.

Soon after admission the patient's vision began to diminish and the development of cataracts was spectacularly rapid. When we were first privileged to see the pa-

tient in the latter part of October she was almost totally blind. At this time her antitetanic therapy consisted of 2 grams of calcium chloride three times per day given in the form of 40 per cent solution. The tetany was under good control. Because of some observations on appetite in deficiencies,[13] dihydrotachysterol was not admin-

FIG. 6. Decreased density of the spine.

istered until the middle of November. The usual rise in serum calcium followed its use. The drug was omitted during the period of recovery from the operation for removal of the cataracts. Thereafter it was resumed at 1 c.c. daily and has been continued at this level ever since, with the addition of varying amounts of calcium lactate. Serum calcium and phosphorus have been essentially normal for the past 9 months to the time of this writing, and there have been no further manifestations of tetany. Her psychiatric status improved steadily.

The patient was discharged from the hospital the latter part of January 1939 and led an inactive life at home almost entirely free of symptoms until her return in May, 1939 for a check-up examination. At this time, though alert and coöpera-

tive, she seemed to have a curious playful diffidence about answering questions directly. Since she flatly refused to be seen by any members of the psychiatric staff, a competent evaluation of her psychiatric status was impossible. She complained only of continued stiffness and soreness of all the muscles of her body but not to any incapacitating degree. She looked quite well. The general physical examination

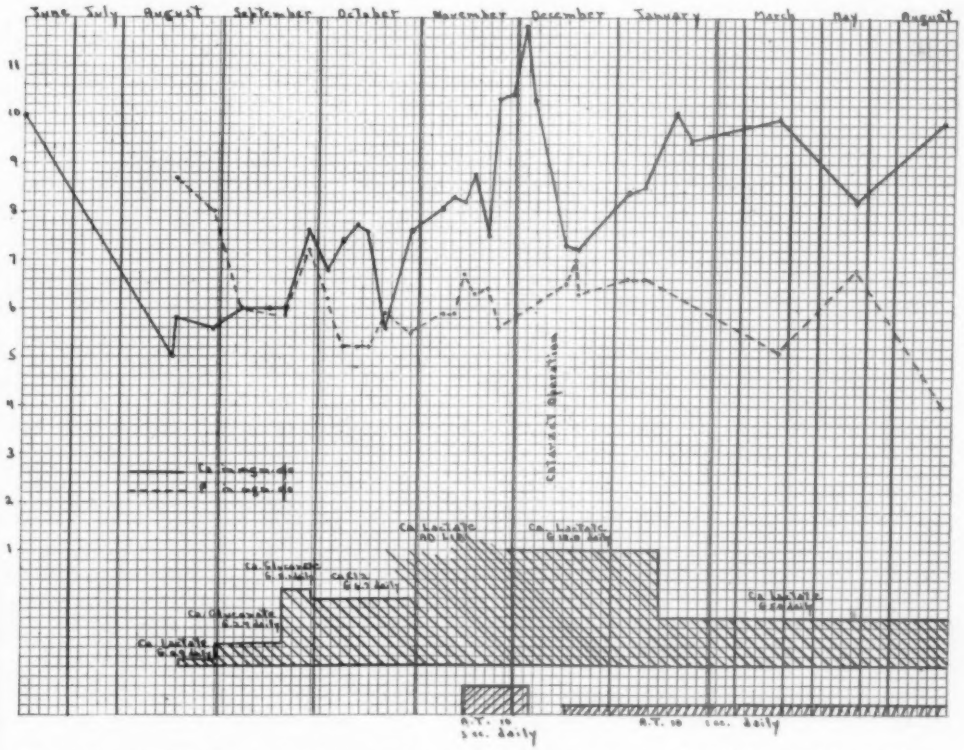

CHART 4. Course of serum calcium and serum phosphorus in case 2 as influenced by calcium therapy and administration of dihydrotachysterol.

proved to be normal with the exception of signs of mild hypertrophic arthritis, which was the reason for her aches and pains in the opinion of Dr. George Eaton, the orthopedic consultant. Chvostek's and Trousseau's signs were absent. Dr. Elliott Randolph, who performed the cataract operations, found the eye status to be entirely satisfactory from the point of view of operative result. Laboratory studies showed the blood morphology to be normal. Serum calcium was 8.2 mg. per cent, phosphate 6.8 mg. per cent, protein 6.9 gm. per cent. Phosphatase 1.5 Bodansky units. Stool and urine examinations were normal and the urinary calcium excretion was low when tested with Sulkowitch's solution.[15] Roentgen-rays showed no change in the density of the bones from the previous examinations. During this admission the patient's sensitivity to parathormone was tested and the response in urinary phosphate excretion was found to be normal.

She left the hospital after these studies were completed, spent an uneventful summer at home, and has resumed her school duties in the fall of 1939. As can be seen from chart 4, with a normal diet, 1 c.c. dihydrotachysterol and 5 gm. calcium lactate per day, her serum calcium and phosphorus have remained essentially normal, and she has been entirely free of tetanic manifestations.

Discussion

There are certain features of this case history that are worthy of discussion, though most are of a purely speculative nature. The most arresting feature is the abrupt onset of tetany within 24 hours after an exciting incident in which there was exposure to a heavy concentration of ammonia fumes. The most conservative interpretation would be that the patient had had mild hypoparathyroidism prior to the explosion incident. Physical fatigue and emotional disturbances are known to make worse the clinical manifestations of hypoparathyroidism. This has been the experience of many previous observers. But when one goes into the patient's past history one finds nothing suggestive of muscular cramps, spasms, or paresthesias, even though she had experienced a severe agitated depression previously. Furthermore the extraordinarily rapid development of bilateral cataracts under observation speaks for an acute disease process. Could the ammonia fumes have played any rôle? We have no clue as to any possible effect on the parathyroid glands of ammonia inhalation but hope to test this hypothesis with some laboratory experiments in the near future. As pointed out by the Massachusetts General Hospital workers,[6] the etiology of idiopathic hypoparathyroidism in youthful patients and elderly patients may be quite different, but in both groups is entirely unknown at the present time.

The status of this patient's skeleton is also of interest. There seemed, by roentgen-ray, to be a general rarefaction of the entire bony structure, but most conspicuous in the bones of the spine. One wonders if perhaps there had been previously present *hyper*parathyroidism with subsequent burning out of the process leaving a deficiency of the internal secretion of the parathyroids. There were, however, no symptoms in her past history suggestive of hyperparathyroidism, and her intake of calcium had always been of such generous proportions as to make it doubtful if skeletal rarefaction would have occurred from moderate hyperparathyroidism. There was no history of vitamin D deficiency. To us the most likely explanation of the skeletal rarefaction is senile osteoporosis. This process, which appears to be a marked reduction in osteoblastic activity, is most commonly seen in women several years after the menopause. Our patient had a menopause artificially induced with radium eight years before she was first seen here. Her serum phosphatase activity was quite low, which would not be out of accord with such a diagnosis. Our impression is, then, that she had senile osteoporosis slowly developing over a course of seven years and an acute recent onset of hypoparathyroidism. It will be interesting to observe the effect of the hypoparathyroidism on the osteoporotic process for, as shown in the previous case of this report, hypoparathyroidism in itself tends to make for excessive bone formation.

Cataracts have been frequently described in association with hypoparathyroidism. However, the rapidity of development and the degree of density of such cataracts vary widely. The physiologic disturbance in hypoparathyroidism which is directly concerned with the cataract formation is entirely unknown, but since identical cataracts occur in association with other diseases in which the serum calcium is lowered but the phosphorus not raised,[21] one would conclude that the low serum calcium level was in some way responsible. It should be emphasized that minimal alterations in the lens may be overlooked; hence examination with the slit-lamp is essential if the incidence of changes in the lens

as a result of parathyroid deficiency is to be estimated accurately. Frequently only a few months' time is required for the development of changes in the lens sufficient to destroy useful vision, as in case 2, whereas in other instances, as in case 1, after many years of hypoparathyroidism only minimal changes can be detected. Perhaps elderly patients tend to develop cataracts more rapidly than juvenile patients, given similar degrees of parathyroid deficiency. The majority of cataracts seen in diseases with low serum calcium are similar to those seen in diabetes and myotonic dystrophy. They are characterized by the subcapsular distribution of the opacities. Vogt described them as linear or fiber-like opacities on the cortex.[16] Other observers [17] have described diffuse or even nuclear changes. As such cataracts develop, the appearance changes until the entire lens may become a gray-white mass. In one of our postoperative hypoparathyroid patients wide clefts were apparent, similar to those of dinitrophenol cataracts. It is of interest that of four postoperative hypoparathyroid patients treated over a period of five years with oral calcium chloride therapy, which produces a mild acidosis, no lens changes were visible even with slit-lamp examination. Though the tetanic symptoms were entirely under control in these patients the serum calcium level rarely rose above 7.5 mg. per cent. The only known treatment for hypoparathyroid cataracts is surgical. To our knowledge restoration of the blood chemical status to normal has never caused reversion of the lens changes.

Summary

Two cases of idiopathic hypoparathyroidism are reported. In the first, a young boy, the disease may have been of congenital origin; in the second the symptoms of tetany occurred abruptly for the first time following an explosion of a refrigerating plant in which the patient was exposed to ammonia fumes. In the juvenile patient roentgen-rays of the bones showed them to be of far greater density than normal and we have evidence to believe that dense bones are the rule in juvenile hypoparathyroid patients. The elderly patient showed greatly decreased bone density and it was thought that she suffered from so-called senile osteoporosis in addition to hypoparathyroidism. Lenticular changes were present in the juvenile patient to only a very slight degree though the disease process had been present many years; the elderly patient developed cataracts under observation with extreme rapidity.

In both patients the sensitivity to parathormone was tested and found normal, showing the disease to be a deficiency of parathormone rather than an increased resistance to it.

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CALCINOSIS UNIVERSALIS *

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THE abnormal deposition of calcium in the body has received considerable attention and study on the part of clinicians, biochemists, dermatologists, and roentgenologists. Instances of abnormal deposition of calcium may be divided into three main groups: progressive myositis ossificans, metastatic calcinosis, and calcinosis (subdivided into calcinosis circumscripta and calcinosis universalis).

* Received for publication June 14, 1939.

Progressive Myositis Ossificans. Mair [1] defines the disease as one of the locomotory system in the growth period of children, affecting not only the muscles but tendons, ligaments, fasciae, and aponeuroses. It is very commonly associated with various congenital abnormalities, the commonest being malformation of the great toes. There is no ossification of muscle but an ossification of fascia and a transformation of fibrous tissue into bone in which ligaments and muscle tendons may participate. The ossification spreads along the fibrous septa and along the tendons, commencing at the bone and extending superficially. The first case was reported by Munchmyer [2] in 1869. Helfrich [3] in 1879 described this rare disease and showed the great prevalence of microdactyly and the absence of the last phalanx of the great toe in 75 per cent of cases. Rosenstirn,[4] who reviewed the literature extensively, also found this deformity very prevalent.

Metastatic Calcinosis. This is a peculiar deposit of calcium found in the heart, lungs, kidneys, and other organs. It does not affect the muscles, fasciae, or subcutaneous tissues. In this condition there is usually a hypercalcemia which is probably of endocrine origin and attributed to the parathyroids.

Calcinosis. Weber [5] in 1878 reported the first case of calcinosis. Verse [6] in 1912 reported a case which he called calcinosis universalis. Steinitz [7] divides the cases of calcinosis into two groups: calcinosis circumscripta and calcinosis universalis. *Calcinosis circumscripta* is the deposit of calcium in the subcutaneous tissue and usually attacks the hands and feet primarily. It rarely occurs in children. *Calcinosis universalis* is the deposit of calcium in the subcutaneous tissue, the muscles, and sometimes along the nerve trunks, especially in the extremities. The hands and feet are not often involved and the number of deposits tends to decrease from the trunk towards the hands and feet. This disease is frequently encountered in children and may be seen even in the first six months of life. In collecting cases of all ages in the literature Steinitz found only 34 cases of calcinosis universalis. It is this extremely rare condition—calcinosis universalis—with which this article is primarily concerned.

Bauer, Marble, and Bennett [8] studied calcinosis universalis extensively and found there was no evidence of any of the unusual abnormalities which are known to produce pathological calcification; namely, chronic inflammation, infarction, hemorrhage, or tissue necrosis. The earliest abnormality noted was the deposition of finely divided calcium particles around the periphery of fat cells, which otherwise histologically appeared to be normal. No evidence of "calcium binding substances within degenerated areas" was seen, since calcification appeared in areas of fat before there was any microscopic evidence of degeneration. The calcium when first retained may have combined with fatty acids but, if so, did not remain in this form, as the analysis of one of these deposits showed that all the calcium could be accounted for as calcium carbonate or tertiary calcium phosphate. They agreed with the conclusion of others that inflammatory changes are not causative factors in these deposits; they considered it reasonable to conclude that calcium and phosphorus metabolism are abnormal in these rare cases of calcification; and they suggested that the increased retention of calcium and phosphorus may be the result of a local cellular condition as yet undetermined. These views relating to the metabolic disturbance in this disease are contrary to the views of Tisdall and Erb,[9] and of Wilens and Derby.[10]

Laboratory Data

York Hospital, February 6, 1934—March 8, 1934

Date	Blood Chemistry					Hematology								Urine						Miscellaneous			
	Non-Fasting Blood Sugar, Mg. %	Fasting Blood Sugar, Mg. %	Blood Serum Phosphorus, Mg. %	Blood Serum Calcium, Mg. %	CO_2 Combining Power, Vol. %	Sedimentation Index, Mm.	HGB, % of Normal (Sahli)	RBC Millions	WBC	Differential WBC, % of Total: Poly., %	Lymph. %	Mononuc. %	Myelocytes, %	Color	Reaction	Sp. G.	Alb.	Sugar	Microscopic Findings	Electrocardiogram	Basal Metab.	Spinal Fluid	Kahn Test
2/ 6/34							68	3,510	11,700	70	26	1	3	Straw	Acid	1.002	Neg.	Neg.	Few squamous cells, mucous shreds and amorph. sed.				
2/ 7/34*						27	58	2.970	13,450														Neg.
2/ 8/34	195.2	111.1	2.97	24.8																	−2 (Check −10)		
2/ 9/34																				Nothing abnormal	+9 (Check +9)		
2/12/34										10	90											U. 3 Ca 10 WBC 90% Polys. 10% Lymph.	
2/13/34				24.2	50																		
2/19/34†				21.5																		Ca 8.4 Mg. %	
2/23/34				23.8																		Ca 10. Mg. %	
3/ 8/34				20.1																			

* Cervical smear showed no gonococci.
† Mantoux negative.

FIG. 1. (February 7, 1934). Roentgenogram of left leg showing deposit of calcium with normal bone structure.

FIG. 2. (February 7, 1934). Roentgenogram of right leg showing extensive deposit of calcium with normal bone structure.

They reasoned that the normal blood values for calcium and phosphorus were not in favor of a metabolic disorder.

Langmead [11] studied the relationship of calcinosis and scleroderma, dermatomyositis and myositis fibrosa, and believed that scleroderma and dermatomyositis are almost inseparable, and that universalis calcinosis is probably a subsequent development.

FIG. 3. (February 7, 1934.) Roentgenogram of right foot and ankle showing deposit of calcium with normal bone structure.

Durham [12] studied the relationship between scleroderma and calcinosis and found that calcinosis was not limited to any one type of scleroderma and that local inflammatory changes are usually not a causative factor, in that the composition of these deposits was calcium phosphate and carbonate, while uric acid was never found. Chemical studies do not indicate any constant variation in either the whole blood or the serum values. There is no oversaturation of calcium salts as is thought to occur in metastatic calcification. Durham states: "It is no-wise clear whether calcinosis with scleroderma results from local metabolic alterations or deranged inorganic metabolism. As in other types of pathologic calcification the colloidal proteins are thought to play a prominent part."

Litchtwitz calls attention to the possible part proteins may play in the induction of calcification. He thinks that the precipitation of colloids in degenerated tissue may bring about a reduction in soluble crystalloids, whereby the more insoluble salts, such as calcium, are precipitated.

Wells [14] pointed out that the calcium is deposited in areas in which carbon dioxide is least abundant.

ONSET OF THE DISEASE

Skossogorenko [15] reported a case of a patient who gave the history of some kind of infection during the latter part of 1922, with high temperature, and who five months later began to "swell." This swelling was "dropsy-like" and

began about the pelvis and femur, spreading uniformly over the entire body. The skin was edematous and pitted. This general edema lasted for three years and was accompanied by diffuse pains, and the patient was unable to move the limbs.

FIG. 4. (February 7, 1934.) Roentgenogram of right foot showing small deposit of calcium with normal bone structure.

Craig and Lyall's [16] case presented the following history: A girl aged five years, three months, was admitted to the hospital on March 25, 1927, on account of palpable lumps in the legs. In February 1926, she developed swelling of the legs from below the ankles to above the knees. No redness was noted in the skin, but the swelling was accompanied by some pain. The joints were a little

FIG. 5. (February 7, 1934). Roentgenogram of left thigh showing a large nodule of calcium and small deposit with normal bone structure.

FIG. 6. (February 7, 1934). Roentgenogram of right thigh showing extensive deposit of calcium with normal bone structure.

stiff, but there were no pains when they were moved. The swelling lasted three months, and then slowly subsided.

Kennedy [17] reported instability and difficulty in walking for two years preceding the onset of calcium deposits.

Logan [18] described a similar case in which Raynaud's syndrome was a prominent feature.

A number of cases have been reported in the literature which are associated with scleroderma, notably those of Durham and Kennedy.

The onset of the disease shows a wide variation, but it is definitely shown that it is more common in children, though it may also be found in the aged. The essential features are acute illness followed by muscular weakness and calcium deposits.

Pathology

Microscopically, the tissue shows a marked infiltration of calcium arranged in globules of varying sizes. The connective tissue is swollen and edematous. Often the calcium salts lie only between the fat cells. The fat cell inside is entirely empty. The endothelium of the vessels is frequently conspicuous and bulges into the lumen. The vessels may show considerable fibrosis of the walls, and some of them may be occluded by this fibrous tissue. The bulk of the lime salt was observed in the fat and fibrous tissue. No giant cells are present and no bone formation. In more advanced cases dense collagenous fibrous tissue, in which calcareous particles are embedded, has replaced the adipose tissue.

Diagnosis

The diagnosis is not difficult when the roentgen-ray is employed, and the findings are definitely pathognomonic of the disease. The calcium is distributed throughout the subcutaneous tissue. There is no evidence of the bone involvement, which is so pronounced in parathyroid dysfunction. The symptoms naturally will depend upon the location of the calcium deposits. It quite frequently happens that the calcium nodules ulcerate through the skin, leaving a sinus which is very slow in healing. The general health of the individual may become affected because activities are limited by the mechanical disturbance which results from the stiffening of the muscles with the calcium salts. Pain may be pronounced when there is pressure on the nerve trunks.

Prognosis

Prognosis is rather unfavorable so far as cure is concerned, and the disease is very progressive. Only one recorded case has gone to autopsy, reported by Durham, the patient having died from some other disease. There was no pathologic change in the parathyroids, though the disease had existed for 37 years.

Treatment

Treatment is of little avail. Nothing has ever been found to benefit this condition. The disease generally continues to progress. Craig and Lyall claimed beneficial results from di-sodium phosphate. Kennedy advised a ketogenic diet. Skossogorenko recommended that ammonium chloride be adminis-

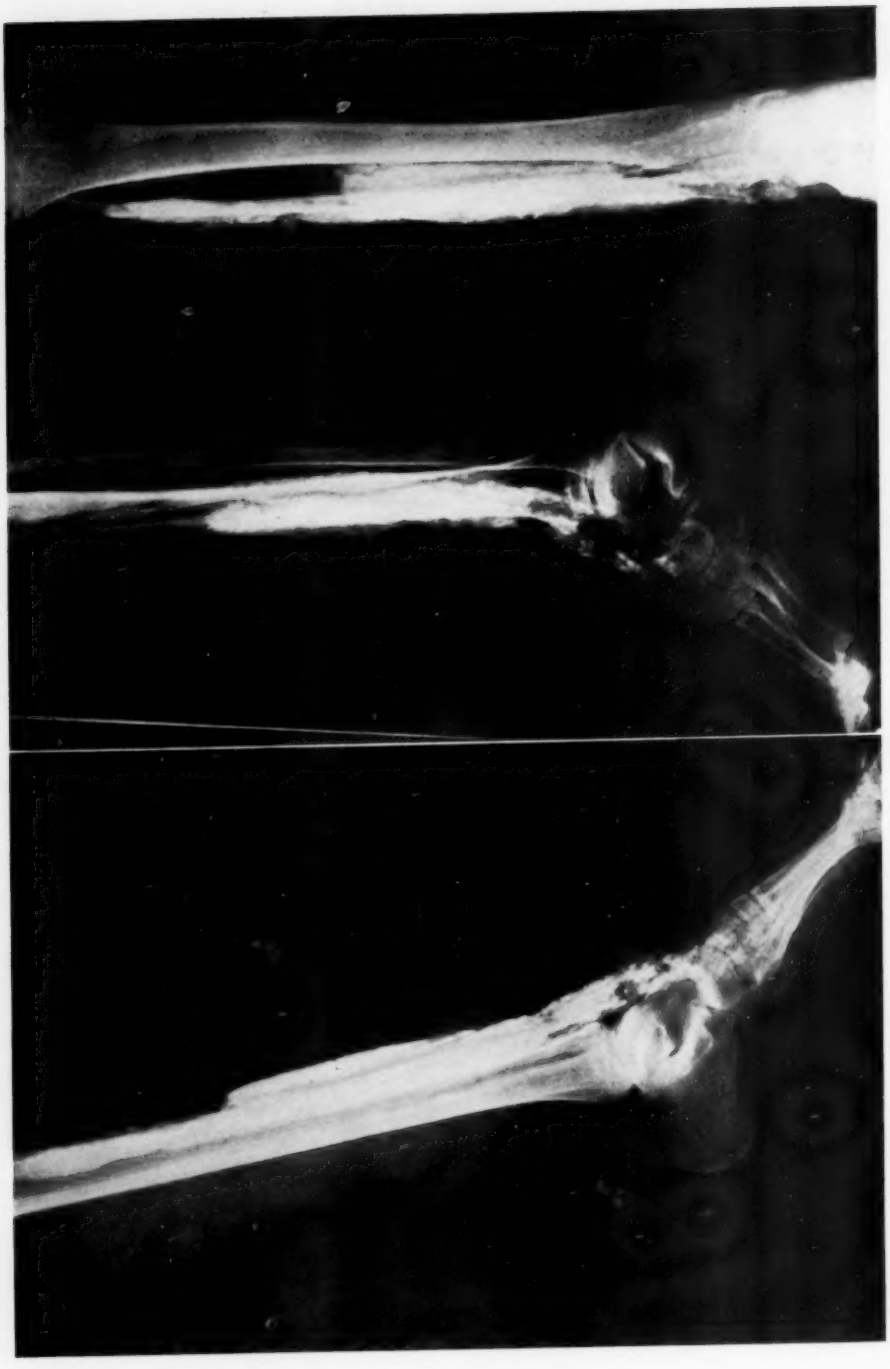

FIG. 7. (March 3, 1934). Roentgenogram of right leg and foot showing no change in deposit of calcium following treatment.

FIG. 8. (May 7, 1934). Roentgenogram of right leg after biopsy showing slight reduction in density of calcium formation, especially in the region of the ankle.

tered internally, with Bier's hyperemia. Hein [19] employed heliotherapy and claimed beneficial results. Parathyroid extract has been used without satisfactory results.

The following case is reported as one of calcinosis universalis:

Case Report

H. S., aged 16 years, female, school child, white, American.

Chief Complaint. Patient was admitted to the Surgical Dispensary of the York Hospital, York, Pennsylvania, on January 16, 1934, exhibiting an ulcer, about 3 cm. in diameter, on the left leg, situated about 8 cm. above the ankle on the outer aspect. There was definite swelling in the lower right leg and also pain in both legs, more especially the right. At this time the patient was referred to the Metabolic Dispensary for more complete studies.

Past Personal History. Customary childhood diseases; occasional attacks of nocturia; menstruation began at 15 years; periods regular, lasting four to six days; present weight is her best weight.

Family History. Father and mother living and well. Patient had four brothers, three living, one having died of pneumonia. There is no history of deformities, dwarfism, or physical abnormalities, and no history of carcinoma, tuberculosis, renal or heart disease, or epilepsy.

Present Illness. The patient fell on the left hip in 1930. The hip became "very sore," and after a year began "draining." It discharged for six months, after which it stopped and the sinus healed. On January 9, 1934, a small ulcer developed on the right knee.

Physical Examination. The patient was admitted to the York Hospital Ward for observation, study, and treatment on February 6, 1934. She was found to be a well-developed, well-nourished girl of 16 years, weight 90 pounds; no pallor; general appearance good. Temperature 99.8°, pulse 80, respirations 20. General examination was negative except for the lower extremities: On the left hip there was a scar of the injury; the left leg presented two ulcers, one above the knee and one on the anterior third of the leg; the right leg presented several ulcers. They were somewhat indurated and were covered with brown scabs. The measurements of the two extremities were apparently the same.

Laboratory findings on admission to the Metabolic Dispensary, January 16, 1934: Non-fasting blood sugar 136 mg. per 100 c.c.; fasting blood sugar 106 mg. per 100 c.c.; urine, acid, sp. gr. 1.008, albumin and sugar absent, microscopic findings essentially negative; Kahn test negative. Blood: red blood cells 2,840,000; white blood cells 18,950; hemoglobin 50 per cent. Differential: transitionals 2 per cent, eosinophiles 1 per cent, polymorphonuclears 76 per cent, lymphocytes 3 per cent, mononuclears, 9 per cent, basophiles 1 per cent, myelocytes 8 per cent.

The following report of biopsy tissue from right leg (April 27, 1934) was made by Dr. Howard M. Jamieson, former pathologist of the York Hospital:

"The specimen consists of three small pieces of firm pinkish white tissue, which together measure 1.0 by 0.5 cm. in size. The tissue as a whole is markedly fibrous and shows numerous small pin-point sized granules of white calcareous material, some of which are merely lying on the surface, and others embedded in the tissue. Gross section shows most of these granules to be on the surface, very few of them being near the center of the masses. All of these granules can very easily be separated from the tissue, giving the impression that they have been merely deposited in their present situations, rather than formed here.

"*Microscopic examination* shows fibrosed muscular tissue and fascia, with

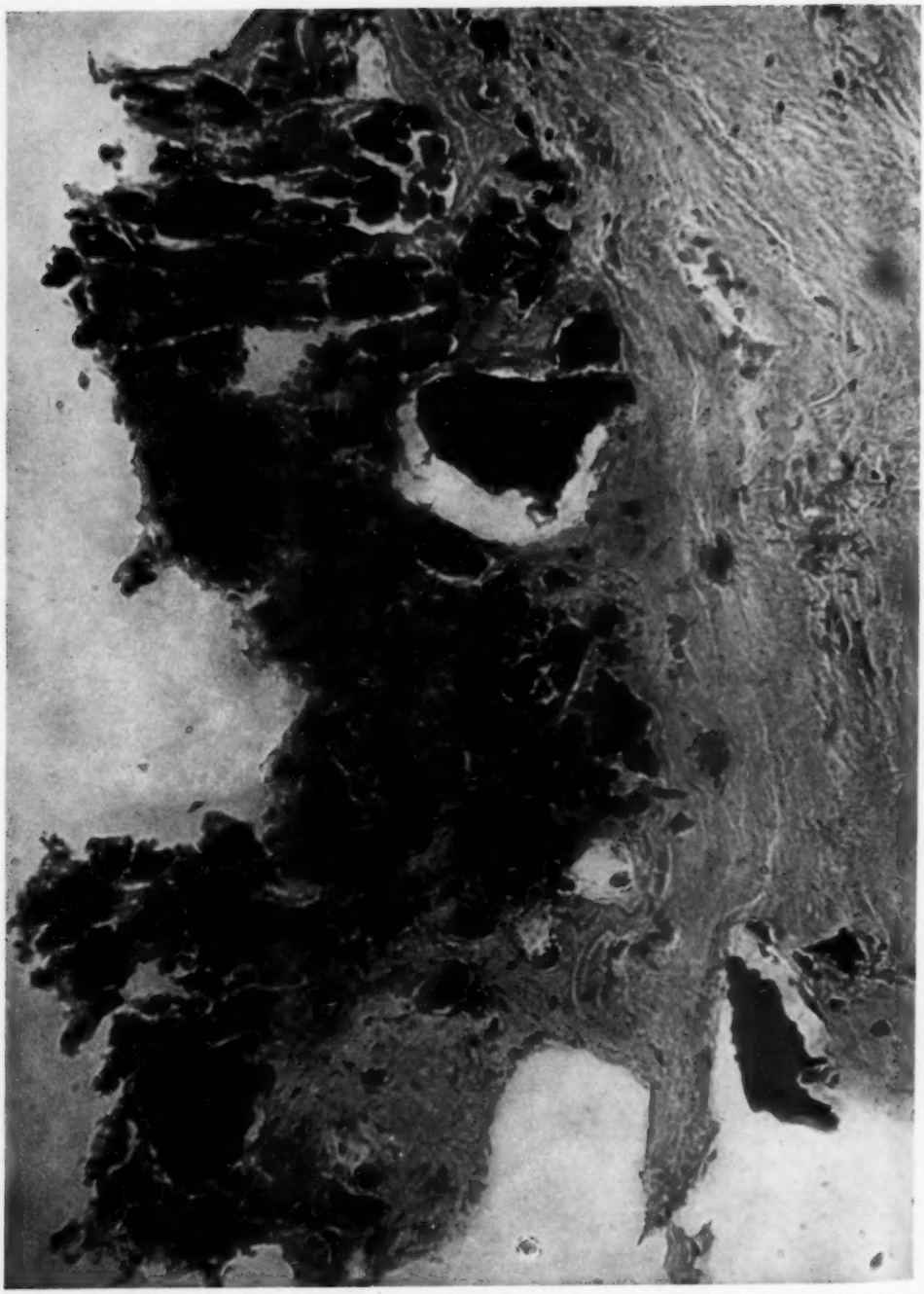

FIG. 9. Photomicrograph of section of subcutaneous tissue removed at biopsy, showing calcareous particles embedded in dense collagenous fibrous tissue. (Made by the late Dr. J. C. Bloodgood.)

numerous small areas of calcification. These areas are all well demarcated and there is no calcium inside the cells, indicating a deposit rather than a formation in situ. Some of these areas are surrounded by zones of fairly dense, small, round-celled infiltration of the chronic irritational type. No true inflammatory change can be seen, and careful search does not reveal any evidence of new bone formation. The condition is one of calcification and not ossification.

"In addition to the above, there was also received about 4.0 c.c. of thick white milky fluid, closely resembling rather thin plaster of Paris, shortly before it sets. Microscopic examination of an emulsion of this fluid shows a few crystals of the phosphate type. Chemical examination shows the fluid to be almost entirely calcium phosphate (about 95 per cent), with traces of chlorides. Fluoroscopic examination of the fluid shows it to be opaque to roentgen-rays.

"From the above microscopic and chemical findings, one must conclude that this is a case in which, due to faulty metabolism, there is a rich deposit of calcium salts, almost entirely phosphate, in the muscle fascia and the more superficial layers of the muscle itself, but no true ossification, and no bone formation of neoplastic type."

Diagnosis: Calcinosis universalis.

Roentgenologic Findings. The patient was referred for the first roentgenological examination on February 7, 1934. The preliminary examination was made of both legs, followed by the examination of the entire body. The right leg shows extensive deposits of calcium extending from the head of the fibula downward along its anterior and external aspects and dorsal aspect of the foot, with a few nodules in the region of the phalanges of the first, fourth, and fifth toes. Two nodules were seen in the lower third of the left leg. In the region of the middle third of the right thigh, in the subcutaneous tissue, there was a rather diffuse deposit of calcium present. Several nodules were seen in the middle third of the left thigh. The bony structure throughout the entire body showed no evidence of decalcification, and there was no deviation from the normal bony structure. No deposits were seen in the abdominal organs.

Roentgenological Diagnosis: Calcinosis universalis.

Roentgenological examination of the right leg and foot made on March 3, 1934 shows no material changes in the calcium deposits. The roentgenological examination made of the right leg and foot on May 7, 1934, after biopsy, shows some reduction in the density of the calcium deposits.

The fluoroscopic examination showed that the fluid which was collected at the time of biopsy was opaque to the roentgen-ray.

Treatment. The patient was given 50 grains of ammonium chloride three times a day, without any noticeable change in the calcium deposit. She was discharged on June 15, 1934. The ulcer which had been present on the legs had healed but at the time the patient left the Hospital, the wound, in the region of the site from which the biopsy had been taken, continued to discharge. The patient returned to the Surgical Dispensary for dressings, and was last seen July 10, 1934. The wound at that time had not entirely healed. The patient failed to return to the Hospital for further treatment after this date.

Summary

Calcinosis universalis should be recognized as a definite clinical, pathological, and roentgenological entity.

The disease consists of the deposit of calcium in the subcutaneous tissue and muscle with reactive fibrosis.

A large percentage of the cases are associated with scleroderma.

The majority of the cases reported show a normal blood calcium.

The roentgenological findings are typical of the disease, which consists of the deposit of calcium in the subcutaneous tissue and muscle, the principal location being in the extremities. There are no bone changes such as are characteristic of hyperparathyroidism.

The disease is probably the result of a disturbance of calcium metabolism. It is progressive but not necessarily fatal. The treatment has not been satisfactory.

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PNEUMOPERITONEUM FOLLOWING USE OF THE FLEXIBLE GASTROSCOPE*

By LEON SCHIFF, M.D., F.A.C.P., RICHARD J. STEVENS,† M.D., and SANDER GOODMAN,† M.D., *Cincinnati, Ohio*

PERFORATION of the stomach is said to occur very infrequently following the use of the flexible gastroscope. According to Schindler and Renshaw,[1] this accident is known to have occurred five times in a total series of four thousand examinations carried out independently by Henning, Gutzeit, Moutier, Benedict, Schloss, and Schindler. In every instance an instrument with a "sponge tip" was used, and in none was the outcome fatal.‡ In two instances the stomach itself was reported to be "apparently normal," and recovery occurred without surgical intervention. In Schindler's own experience perforation has occurred in three cases of gastric carcinoma. The perforations, however, involved portions of the stomach wall not invaded by the growth, were twice located high on the posterior wall, and once on the anterior wall near the greater curvature. As he was able to see the peritoneum in two of these cases, he believed that in these the perforations were caused by the tip of the instrument and were not due to overdistention of the stomach with air.

In a study dealing with various factors influencing perforation of the stomach with the flexible gastroscope, Schindler and Renshaw conclude that the tip of the instrument is the most important. They showed experimentally that with the "sponge tip" there is greater friction on the stomach surface and the pressure of the advancing gastroscope is, therefore, more apt to be localized to the stomach wall in contact with the tip. On the other hand, "a long rubber finger directs the instrument in the line of least resistance and initiates bending of the flexible portion thereby distributing pressure on the stomach surface more evenly." They therefore advise the universal use of a rubber finger tip 4 to 6 cm. in length. However, even with the use of such a tip, pneumoperitoneum may result as evidenced by the following case report.§

CASE REPORT

Clinical History: R. B., white male, aged 77, was admitted to the Cincinnati General Hospital, March 16, 1938, because of dyspnea and weakness. In 1929 he was found to have hypochromic anemia with achlorhydria. Although symptomatic improvement followed liver therapy at that time, there was no reticulocyte increase.

Physical Findings: He was somewhat underweight and was suffering with a mild senile psychosis. The sclerae were not jaundiced. There was marked pallor of the conjunctivae. The papillae of the tongue were prominent. The lungs were emphysematous. The heart was moderately enlarged to the left, and a systolic murmur was heard at the apex. The blood pressure was 170 systolic and 100 diastolic.

* Received for publication August 3, 1939.

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† Justin A. Rollman Fellows in Internal Medicine, 1938–1939, and 1937–1938, respectively.

‡ Bergh, Bowers, and Wangensteen [2] mention one instance of perforation in their clinic. Their patient developed pneumoperitoneum without evidence of peritonitis and recovered without operation.

§ This represents the only recognized instance of perforation in our experience which includes more than five hundred examinations.

The upper border of the liver was at the fifth intercostal space in the mid-clavicular line; the edge was two fingers'-breadth below the right costal margin in the mid-clavicular line. The spleen was not felt. Appreciation of vibration was decreased in the lower extremities. There was minimal edema of both ankles.

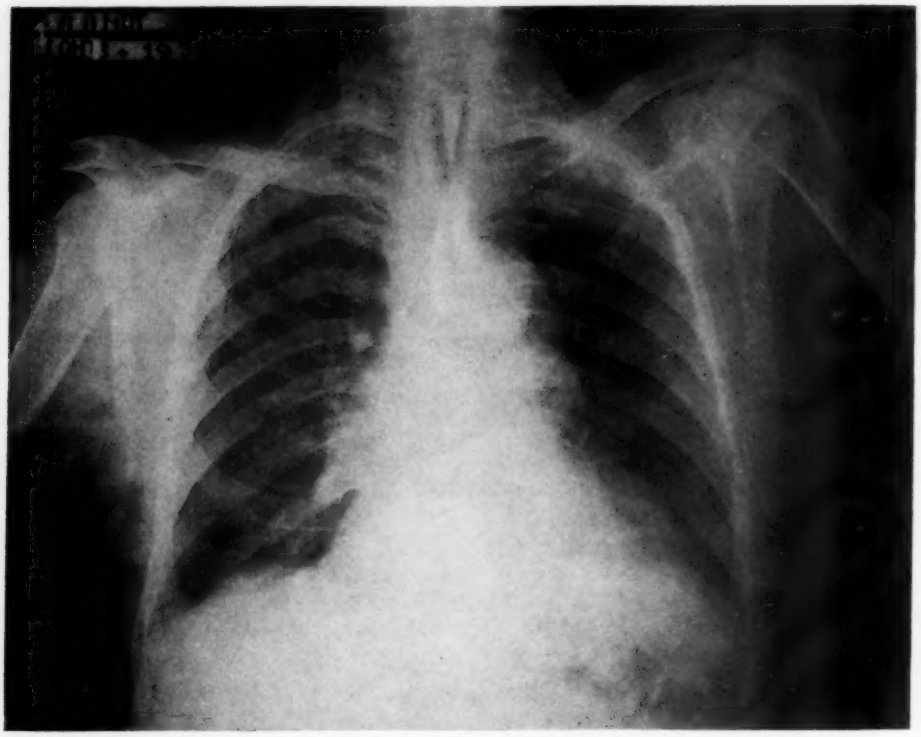

FIG. 1. Film of chest made March 19, 1938, two days prior to gastroscopy.

Laboratory Findings: Hemoglobin 4.2 gm. per 100 c.c.; red blood count 2,830,000; white blood count 7,800; hematocrit 20; mean corpuscular volume 71. The urinalysis was normal. Chemical tests of the stools for blood were negative. Following histamine there was no free hydrochloric acid in the gastric secretion. The blood Kahn test was negative.

On March 19, 1938, a roentgenogram of the chest was taken which showed "only moderate enlargement of the cardiopericardial shadow." The diaphragm appeared normal (figure 1).

On March 21, 1938, after the patient had had nothing to eat or drink for 12 hours, gastroscopic examination was done with the flexible Wolf-Schindler instrument with a rubber, finger-like tip measuring 4.8 cm. in length. (Twenty minutes before the examination he had received a hypodermic injection of morphine sulfate gr. ⅙ and atropine sulfate gr. $\frac{1}{150}$.) The instrument was readily passed. The patient coöperated excellently. The stomach was inflated with air in the usual manner. The pylorus was normal. There was pallor of the mucosa. The rugae were absent. Numerous branching vessels were seen in the body of the stomach. It was evident that diffuse atrophic gastritis was present. Visibility was excellent throughout the entire examination. The peritoneum was not seen, nor was there any sudden defla-

tion of the stomach as Schindler has observed in perforation of the stomach wall by the instrument.[3] Incidentally, a finger-like projection was seen to dip into the antrum in the direction of the pylorus (figure 2). It was at first believed to represent a benign polyp but was found to be the end of the instrument itself when it was covered

FIG. 2. Photograph of drawing showing tip of instrument mistaken for benign polyp in antrum.

with a strip of adhesive and passed into another patient. The tip had become extremely flexible and had probably been bent upon itself.

After two hours had elapsed following completion of the gastroscopic examination, the patient was permitted to eat the regular hospital diet and take fluids as desired. Part of the day was spent up and about the ward. There were no subjective complaints. His temperature was normal. A white count on March 23 was 10,000. On March 25, four days after the gastroscopic examination, he was sent to the roentgen-ray department for a gastrointestinal series.† No barium was given as Dr. H. Senturia, on preliminary fluoroscopy, noticed that there was a layer of air about 1½ cm. in depth under each dome of the diaphragm (figure 3). The patient was immediately returned to the ward and examined. The abdomen was flaccid and free of tenderness. There was some reduction of liver dullness. He offered no complaints. The white blood count was 7,600 with a normal differential count. He was seen in consultation with Dr. Max Zinninger who advised against surgical intervention. A bland meat-free puréed diet was prescribed, and the patient was allowed to get out of bed as desired.

One month later a gastrointestinal roentgen-ray series was negative. At this time there was no demonstrable air below the diaphragm. His red blood count had risen to normal after oral administration of iron, and he was discharged on May 5, 1938. He has been followed in the out-patient department, and, when last seen on March 13, 1939, he was feeling quite well.

Whether the pneumoperitoneum was due to the instrument penetrating the stomach wall or to overdistention of the stomach with air, was, of course, not

† Ordinarily gastroscopic examinations are carried out after previous roentgen-ray examination of the gastrointestinal tract. This order was reversed in this case, because, in another patient barium was still present in the stomach four days after it had been given and had prevented a satisfactory gastroscopic examination.

established.* The stomach wall was probably thinner than normal because of atrophy of the mucosa. More pressure than usual was probably exerted on the posterior wall of the stomach near the greater curvature as evidenced by the fact that the tip of the instrument was bent upon itself. However, there was no

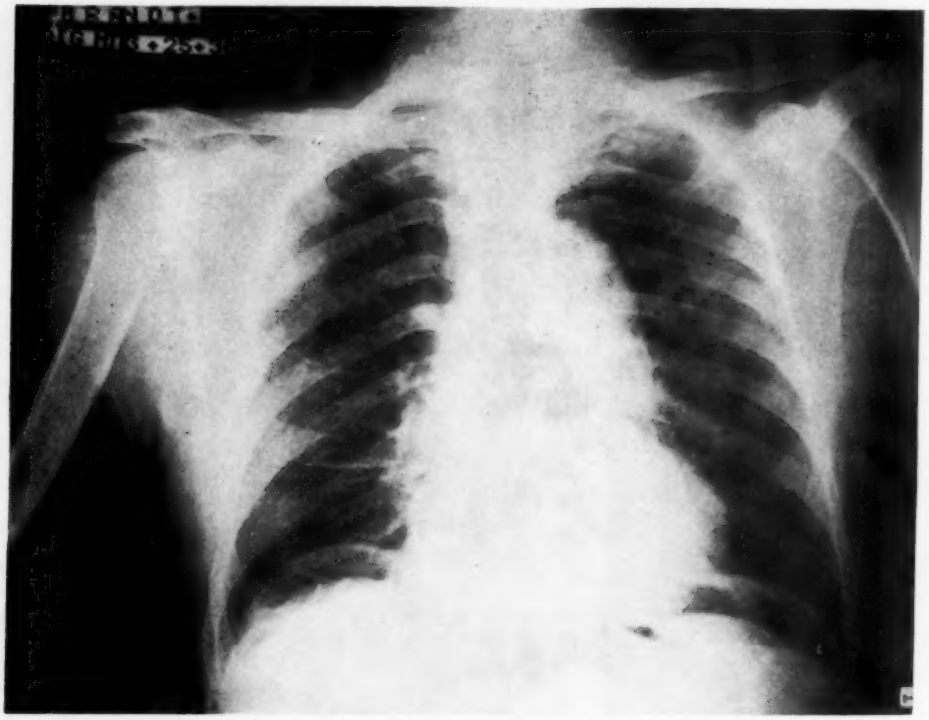

FIG. 3. Film of chest made four days after gastroscopy, showing free air below diaphragm.

deflation of the stomach nor was the peritoneum seen as might have been expected had the instrument itself penetrated the stomach wall.

The accidental discovery of the pneumoperitoneum is remarkable. This suggests that this complication may occur more frequently than is generally believed. It is possible that the absence of pain may have been partly due to the hypodermic injection which preceded the examination. Failure of peritonitis to develop in spite of the ingestion of food and water soon after the gastroscopic examination is deserving of comment, as is the patient's spontaneous recovery.

Of much interest in this connection is the report of Bergh, Bowers, and Wangensteen [2] who found that in a group of 29 experimental animals the mortality following perforation of the empty stomach was only 6.9 per cent. In their earlier studies water was withheld for 24 hours and food for 48 hours after the perforations were produced, but in later studies the animals were al-

* Since this paper was submitted, RUMBALL, J. M., in the Jr. Am. Med. Assoc., 1939, cxiii, 2053, has reported perforation of the jejunum with a flexible gastroscope equipped with a rubber finger-tip.

lowed to take food and water at will. On the other hand, when the stomach contained food at the time of perforation, the mortality rose to 86.7 per cent.

Summary

Pneumoperitoneum may follow the use of the flexible gastroscope with the finger-like rubber tip. It may develop in the absence of any symptoms, may be unaccompanied by any signs of peritonitis, and may disappear without surgical intervention in spite of the administration of food and water shortly after withdrawal of the instrument.

A case is described which marks the seventh * reported instance of perforation of the stomach following use of the flexible gastroscope. As in the other reported cases, the outcome was not fatal.

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* Since this paper was submitted, Schindler, R., in Am. Jr. Digest. Dis., 1940, vii, 293–295, has reported eight instances of perforation of the stomach, one of perforation of the jejunum, and one of perforation of the esophagus following use of the flexible gastroscope.

EDITORIAL

THE LIVER AND ESSENTIAL NUTRIENT FACTORS

It has long been recognized by experimental workers and clinicians that the liver can be protected against the action of hepatotoxic agents and the consequences of biliary obstruction by dietetic means. The optimal diet commonly prescribed for patients who have hepatic disease is high in carbohydrate and low in fat; the protein requirements are made up largely from vegetable sources, eggs and milk. The high carbohydrate content, of course, is intended to favor storage of glycogen and the low fat content to prevent excessive deposition of fat within the liver. It has been demonstrated that meat protein and its extractives seem to exert an unfavorable effect on the injured liver but recognizing the need for an adequate intake of protein, other sources have been drawn on to maintain nitrogen equilibrium. It may be assumed that a qualitative difference exists between various proteins as far as their effect on the liver is concerned; in fact, experimental evidence indicates that under certain conditions protein may function in a protective manner. To date, no studies have been reported on the possible effects of specific amino acids contained in animal protein as contrasted to those derived from vegetable sources, whites of eggs and milk; perhaps some amino acids have a specific protective effect on hepatic cells and others exercise an opposite influence.

Recent studies indicate that other basic requirements are probably of considerable importance and must be met in order to maintain normal hepatic structure. Rich and Hamilton [1] reported that cirrhosis of the liver developed among rabbits maintained on a diet of synthetic composition and without any natural sources of the vitamin B complex. Similar hepatic lesions also were observed when thiamin chloride, riboflavin, pyridoxine hydrochloride, nicotinic acid and vitamin E were added to the diet in quantities sufficient for normal maintenance. Further studies by these investigators revealed that an adequate amount of yeast added to the diet prevented the development of this type of cirrhosis and that increasing the amounts of the aforementioned components of the vitamin B complex had a partially protective effect. They concluded that some factor in yeast is necessary for prevention of pathologic change in the parenchyma of the liver of rabbits at least. In their recent report they called attention to the observations of György and Goldblatt,[2] who demonstrated that hepatic necrosis develops in rats maintained on a diet deficient in yeast. The specific substance in yeast which produces this effect has not yet been identified.

Choline also may exert some protective effect of a peculiar nature on the

[1] Rich, A. R., and Hamilton, J. D.: Further studies on cirrhosis of the liver produced by a dietary deficiency, Trans. Assoc. Am. Phys., 1940, lv, 133–139.

[2] György, P., and Goldblatt, H.: Hepatic injury on nutritional basis in rats, Jr. Exper. Med., 1939, lxx, 185–192.

liver. Best and his co-workers [3, 4, 5] investigated this matter thoroughly and in a long series of experiments revealed that an adequate intake of choline prevents fatty metamorphosis of the liver which ordinarily occurs in animals maintained on a high fat diet; they further demonstrated that the deposits of fat in the liver, which followed intoxication with carbon tetrachloride, were removed more rapidly when choline was added to the diet of experimental animals than was the case in a series of control animals.

Griffith and Wade [6, 7] during the past year published additional reports on the effect of deprivation of choline. In observations made on rats they found that a deficiency of choline, in addition to producing a fatty liver, also arrested growth and caused regression of the thymus gland, splenomegaly and enlargement and hemorrhagic degeneration of the kidneys. Small amounts of choline prevented all the pathologic picture except deposition of fat in the liver. They also noted that the addition of cystine to the diet increased requirements for choline and that methionine had an opposite effect. From the foregoing, it is apparent that choline acts under some dietary conditions as a protective substance for the hepatic parenchyma and that its activity may be affected by the presence of certain specific amino acids.

Clinical evidence to support these observations has not been supplied to date but there is much to suggest that the patient who has alcoholic cirrhosis suffers not only from the hepatotoxic effect of alcohol but also from an actual dietary deficiency, the exact nature of which is not yet definitely known but which may involve some component of the vitamin B complex. Treatment directed toward correcting the latter condition by an optimal diet and generous supplies of the vitamin B complex has been productive of surprisingly good results in certain cases.

The matter of secondary deficiency in essential nutrient factors also has been studied in connection with hepatic disease. Good evidence indicates that the liver is a great storage depot for vitamins and perhaps for provitamins; its normally high content of vitamins A and D is well known, as is the fact that it is one of the principal storehouses for vitamin C. It likewise stores the vitamin B complex or at least certain portions of it. It is natural to suppose that in advanced hepatic disease a state of deficiency in respect to one or more of these vitamins may develop.

So far as the fat soluble vitamins are concerned, it is well known that night blindness may develop in the course of hepatic disease. As Patek [8]

[3] Barrett, H. M., Best, C. H., MacLean, D. L., and Ridout, J. H.: The effect of choline on the fatty liver of carbon tetrachloride poisoning, Jr. Physiol., 1939, xcvii, 103–106.

[4] Best, C. H., Channon, H. J., and Ridout, J. H.: Choline and the dietary production of fatty livers, Jr. Physiol., 1934, lxxxi, 409–421.

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[6] Griffith, W. H., and Wade, N. J.: Some effects of low choline diets, Proc. Soc. Exper. Biol. and Med., 1939, xli, 188–190.

[7] Griffith, W. H., and Wade, N. J.: Choline metabolism. I. The occurrence and prevention of hemorrhagic degeneration in young rats on a low choline diet, Jr. Biol. Chem., 1939, cxxxi, 567–577.

[8] Patek, A. J., Jr., and Haig, C.: Occurrence of abnormal dark adaptation and its relation to vitamin A metabolism in patients with cirrhosis of the liver, Jr. Clin. Invest., 1939, xviii, 609–616.

has shown, the defect is not a matter of deficiency of vitamin A alone, for sufficient vitamin A to correct nyctalopia of patients without hepatic injury is ineffectual against night blindness in cirrhotic patients. Furthermore, the provitamin beta-carotene is also ineffective. The latter indicates that the difficulty probably lies in the inability of the liver to manufacture vitamin A from sources in which it is normally supplied to the body. A somewhat similar condition exists in respect to vitamin D. As Heymann [9] has demonstrated, rats poisoned with carbon tetrachloride and maintained on a rachitic diet required enormous doses of vitamin D to correct the bony changes present. It is also known that patients who have cirrhosis of long standing may develop deficiency of vitamin D which manifests itself as osteoporosis; in extreme cases this condition may be sufficient to produce actual osteomalacia with pathologic fractures. For such patients a high intake of vitamin D and calcium is neither protective nor curative. In regard to the fat soluble, antihemorrhagic vitamin K, the evidence is even more striking. When hepatic damage has reached an advanced stage, neither the vitamin itself nor its synthetic analogues can be utilized in the formation of prothrombin. This fact has been demonstrated fully by both clinical [10] and experimental [11] studies.

Knowledge in regard to deficiencies in the water soluble vitamins is considerably more meager. True deficiency of vitamin C is rare in hepatic disease, although low levels of cevitamic acid in the urine and plasma may be encountered occasionally. Such specific deficiency states as cheilosis, pellagra and peripheral neuritis are also decidedly uncommon. Some recent clinical evidence indicates that hepatic insufficiency, especially that which is associated with hepatic coma, may be due to a deficiency of thiamin chloride and nicotinic acid; at least, patients in coma have sometimes been miraculously revived by administration of these substances.

Certain obvious therapeutic implications arise from a consideration of the experiments described. The first is that certain types of dietary deficiency must be considered as playing an etiologic rôle in laying the groundwork for hepatic injury; the second is that hepatic disease, once it is present, renders the affected person liable to secondary deficiency of vitamin D. This is apparently more likely to involve the fat soluble compounds. It must be recalled that our clinical knowledge of specific deficiencies arising from failure of utilization of certain portions of the vitamin B complex, notably choline, is far from complete and that the influence of certain amino acids on the liver has yet to be ascertained. The problem is one of increasing complexity and yet in its solution may be the clue to some of the unsolved problems in the clinical physiology of the liver.

ALBERT M. SNELL.

[9] HEYMANN, WALTER: Importance of the liver for the antirachitic efficacy of vitamin D, Proc. Soc. Exper. Biol. and Med., 1937, xxxvi, 812.

[10] BOLLMAN, J. L., BUTT, H. R., and SNELL, A. M.: The influence of the liver on the utilization of vitamin K, Jr. Am. Med. Assoc., 1940, cxv, 1087–1090.

[11] FLYNN, J. E., and WARNER, E. D.: Prothrombin levels and synthetic vitamin K in obstructive jaundice of rats, Proc. Soc. Exper. Biol. and Med., 1940, xliii, 190–194.

REVIEWS

The Rectum and Colon. By E. Parker Hayden, A.B., M.D., F.A.C.S., Assistant in Surgery in the Harvard Medical School, Boston, Mass., Assistant Surgeon and Chief of Rectal Clinic, Massachusetts General Hospital, Boston, Mass. 434 pages; 15.5 × 24 cm. Lea and Febiger, Philadelphia. 1939. Price, $5.50.

This short book on the rectum and colon is written in a form that amounts to a series of monographs based on cases seen at the Massachusetts General Hospital Clinic and in the author's private practice. Because of this it tends to be rather incomplete in its discussion of certain conditions that are not prevalent in the Boston area, such as lympho-pathia venerea and the rarer disease entities in which the series from such a single source are bound to be small. However, most sections are quite complete and well written. The sections on anatomy and methods of examination are particularly good. The author's discussion of the treatment of hemorrhoids deserves attention. He gives one of the few good recent reports comparing the operative with the injection methods. He reaches the following conclusion: "Since that time (1928) there has been a gradual rise in the number of cases operated upon as our early hopes with regard to permanent results of injection treatment became modified." I feel that this statement is typical of most people's experience with the new wave of injection methods and solutions. So many people seem to think that injection is something new and a cure all, when really it is a mere recrudescence of a very old and several times discarded procedure. There is no question in anybody's mind concerning the author's statement that "Small and moderate sized uncomplicated internal piles giving symptoms of bleeding alone, or bleeding and protrusion with spontaneous retraction, are best suited to this method of treatment." The trouble is that too few people who use the method are capable of making this differentiation, or because of the *apparent* ease and safety of injection they do not attempt to make it. This is a very timely and carefully analyzed report with good follow-up of the patients treated by both methods.

In the field of major operative procedures on the right side of the colon and the segment of bowel between the recto-sigmoid junction and the anal margin the author seems to favor two-stage operations much more than is the case in certain other sections of the country. Not quite enough space comparatively, seems to be given to the major operations on the colon, together with the pre- and post-operative care of such patients.

J. C. O.

Diseases of Infancy and Childhood. By the late L. Emmett Holt, M.D., and John Howland, M.D., Revised by L. Emmett Holt, Jr., M.D., and Rustin McIntosh, M.D. Eleventh Edition. 1421 pages; 25 × 17 cm. D. Appleton-Century Co., New York. 1940. Price, $10.00.

The eleventh edition of this well known book is definitely within its usual excellent standards.

This edition, however, is somewhat different from its predecessors in that approximately 35 collaborators with information in specialized pediatric fields have contributed. With these collaborators there has been no loss of uniformity of style nor thoroughness.

The arrangement of the book has not changed in any essential detail. It now contains approximately 1450 pages divided into 21 sections, a new section "Diseases of the Eyes" having been added. "Premature Infants" is now given a separate section, and "Diseases of the Blood" is now grouped under the "Circulatory System."

Revision varying from a very minor to a very marked degree is evident through the entire book. Sections dealing with diseases of the newborn, prematures, nutrition, and many other subjects have undergone drastic changes. Many new topics have been added.

The book cannot be too strongly recommended to students and all others with specialized interest in pediatrics. It contains all the newer concepts of disease and therapy in their most recent form, and is quite different from many textbooks which are old at the time of publication.

W. M. S.

Über die integrative Natur der normalen Harnbildung. In Three Parts. By GÖSTA EKEHORN, Helsingfors. Part I, 616 pages; Part II, 418 pages; Part III, 292 pages; 15 × 24 cm. Mercators Tryckeri, Helsingfors. 1938.

Those who desire a scientific survey of recent work on kidney physiology should avoid these three volumes. They offer an extraordinarily voluminous and tedious argument (1389 pages), very poorly related to recent experimental work, and leading to some erroneous conclusions. The author attempts to discuss all phases of the filtration-reabsorption theory, and is particularly concerned with the forces involved in tubular activity. Unfortunately he gives no experimental evidence of his own, and is unfamiliar with much relevant recent literature. He places great emphasis upon the old paper of Marshall and Kolls (1919) in which the results of kidney denervation were studied and upon the work of Rehberg (1926) in which the U/P ratio of creatinine was first used to calculate plasma clearances in man. The author is apparently unaware that it is now known (Shannon, 1935) that in the human kidney creatinine is in part secreted by the tubules and cannot be used, without correction, to calculate the clearances of other substances. He seems to be only dimly aware of the present use of xylose and inulin in clearance work.

One example of the unscientific character of the author's argument may be given. He accepts Keller's description of positively charged granules embedded in otherwise negatively charged cells of the proximal convoluted tubules. He argues that electrolytes must be reabsorbed in this segment since charged structures of both signs are available simultaneously to attract anions and cations. Glucose, he is driven to conclude, must be here reabsorbed in its enol form (a weak acid), attracted by the positively charged granules. The distal tubules, bearing only negative charges, must, he thinks, be able to absorb only positively charged water and non-electrolytes, like urea. Such naive electrostatic philosophy is directly contradicted by the experimental results of Walker, Hudson, Findley and Richards (1937) who have demonstrated that, in the amphibian kidney at least, the distal tubules are the main site of electrolyte reabsorption and acid-base changes. No references to this paper and other related work are given.

The author needs to learn that the problems of kidney function cannot be resolved by weaving dreams concerning the organ. Here, as always, the only sure approach to understanding is by the experimental road.

W. R. A.

Neurology. By S. A. KINNIER WILSON, M.A., M.D., D.Sc. Edited by A. NINIAN BRUCE, F.R.C.P., D.Sc., M.D., Consulting Physician Bangour Mental Hospital and St. Andrew's Hospital, Stirches. Two volumes, lxvl + 1836 pages, 348 illustrations. Williams & Wilkins Co., Baltimore. Price, $21.00.

This large two volume work is a comprehensive survey of clinical neurology. Written in the clear pungent style so characteristic of Kinnier Wilson, it is a credit to British neurology. The many hundreds of references in the form of footnotes

show a prodigious amount of work. The manuscript was not completed at the time of the author's unexpected death. However, full particulars were found among his papers regarding the plan of the book. The task of compiling and editing the manuscript and revising and adding to the references was done by A. Ninian Bruce, to whom thanks are due for carrying out a difficult task so well. Anyone who knew Wilson will agree that the forceful style, the use of many new words, and the strong opinions expressed are evidence that the manuscript has not been changed by the editor.

Many chapters are excellent, particularly those which deal with subjects in which the author was especially interested or ones which he considered of paramount importance. These include such subjects as lenticular degeneration, paralysis agitans and other related syndromes, epilepsy and syphilis of the nervous system. Considerable attention is devoted to special forms of toxicosis of the nervous system such as alcoholism, Indian hemp intoxication, carbon monoxide poisoning, etc.

There are several important omissions probably due to lack of completion of the manuscript. There is no discussion of aphasia or apraxia, nor are the syndromes associated with occlusion of important cerebral arteries, such as the anterior and middle cerebrals and the posterior-inferior cerebellar, presented. Despite these omissions, the work is a great one because of its value as a reference work and the many admirable descriptions of disease entities. It should be of great value to anyone interested in the nervous system and should be in the hands of every neurologist and internist.

A. C. G.

Tuberculosis of the Bone and Joint. By G. R. GIRDLESTONE, M.A., B.M. Oxon., F.R.C.S. Eng. 265 pages; 25 × 17 cm. Oxford University Press, New York. 1940. Price, $8.75.

The present day conception of bone and joint tuberculosis is the result of a gradual evolution of ideas on this subject. Skeletal tuberculosis is now considered one manifestation of a tuberculous infection which has other foci elsewhere in the body. This conception brings this form of the disease into closer connection with the field of work of the internist.

Medical men hence will be particularly interested in the earlier chapters of Mr. Girdlestone's book in which the author discusses these relations of skeletal tuberculosis to tuberculosis in other situations. The sections on the diagnosis of bone and joint tuberculosis will also be of interest. More emphasis could be laid upon the general radiological appearances of a tuberculous joint as compared to other chronic lesions.

The remainder of the book is devoted to the more exclusively orthopedic aspects of tuberculosis of bones and joints. Girdlestone is in accord with many other orthopedic surgeons as to the gloomy prospect of obtaining a useful range of motion and subsidence of the lesion. He, too, favors operative fusion to completely immobilize a joint as the best means today of obtaining a relative cure. On the other hand he gives his end result figures with the conservative or non-operative measures and compares them with those obtained by more radical procedures. Many works on this subject emphasize the one phase and ignore the other, but it can be said of Mr. Girdlestone that he approaches the subject with an open mind and states his results fairly, with the preponderance of evidence favoring the radical cure of tubercular skeletal lesions by operative fusion of the joint.

H. F. U.

COLLEGE NEWS NOTES

Publication of the History of the American College of Physicians

On December 15, 1940, Dr. William Gerry Morgan, Washington, D. C., College Historian, presented to the Board of Regents the completed volume of "The American College of Physicians—Its First Quarter Century," a work on which the Historian had been engaged for the past four years. The History was authorized during the Presidency of Dr. Ernest B. Bradley in 1936, and the preparation of the volume required long and arduous review of the transactions of the College from its initiation in 1915. Dr. Morgan called upon other individuals to assist in the preparation of special chapters on matters with which they were especially familiar, or on which they were especially competent to write. The contents include: "Preface," by Dr. George Morris Piersol, Secretary-General; "The Founding of the College," Dr. William Gerry Morgan; "The Presidents of the College," Dr. William Gerry Morgan; "Other Officers," including The Secretary-Generals, The Treasurers, The Editors of the Journal, The Chairman of the Board of Governors and the Executive Secretary, Dr. William Gerry Morgan; "The Constitution and By-Laws" by Mr. Edward R. Loveland, Executive Secretary; "Financial Record of the College" by Mr. Edward R. Loveland, Executive Secretary; "The Publications of the College" by Dr. Maurice C. Pincoffs, Editor of the Annals of Internal Medicine; "The American Board of Internal Medicine" by Dr. Walter L. Bierring, first Chairman of that Board; "My Recollections of the Period," 1925–29, by Dr. Charles F. Martin, former President of the College; "The History of Recent Years" by Dr. James Alex. Miller, former President of the College. Part II of the book is devoted to the chronology of the College, consisting of an abstract from the past Minutes of the College, tracing the actual developments, the formation of policies and the growth and expansion of the organization to the end of the Cleveland Annual Session, 1940. As a concluding chapter, there is a description of the present objectives, activities, administration and requirements of admission.

The book is an example of practical, artistic and good book-making. It is bound in green buckram, stamped in gold with the Corporate Seal of the College. The paper stock represents one of the finest grade of dull coated paper with a complete absence of glare or reflection. The type was selected from a type face and point easily read.

When the publication of the History was first authorized, the Board of Regents directed that it be sent to all Fellows and Masters of the College in good standing. Upon examination of the volume in its completed form, the Board of Regents expressed the desire to give a copy of the History also to all Associates of the College in good standing, and to have a sufficient reserve stock to furnish a copy gratis to every new physician elected to the College during the next three years.

The volume may be purchased by individuals, societies or libraries at the nominal cost of $2.00, postpaid.

Gifts to the College Library

The following gifts to the College Library of publications by members are gratefully acknowledged:

Books

Dr. Edgar V. Allen, F.A.C.P., Rochester, Minn.—"Nelson's Loose-Leaf Specialties in Medical Practice," Volumes I and II;
Capt. Harry G. Armstrong (Associate), (MC), U.S.A., Toronto, Can.—"Principles and Practice of Aviation Medicine";
Dr. Leon H. Collins, Jr., F.A.C.P., Philadelphia, Pa.—"Internal Medicine in Dental Practice";
Dr. D. Sclater Lewis, F.A.C.P., Westmount, Que.—"Pharmacopoeia and Clinical Methods of the Teaching Hospitals, McGill University."

Reprints

Dr. Nathan Blumberg, F.A.C.P., Philadelphia, Pa.—1 reprint;
Lieut. Col. Joseph R. Darnall, F.A.C.P. (MC), U. S. A., Washington, D. C.—1 reprint;
Lieut. Col. Daniel B. Faust, F.A.C.P. (MC), U. S. A., Denver, Colo.—2 reprints;
Dr. Francis R. Finnegan (Associate), St. Louis, Mo.—2 reprints;
Dr. John Arthur Foley, F.A.C.P., Boston, Mass.—1 reprint;
Dr. Irvin Reginald Fox (Associate), Eugene, Ore.—1 reprint;
Dr. Paul John Hanzlik, F.A.C.P., San Francisco, Calif.—25 reprints;
Dr. Harold Jerome Harris (Associate), Westport, N. Y.—2 reprints;
Dr. Arthur A. Herold, F.A.C.P., Shreveport, La.—2 reprints;
Dr. Morrill L. Ilsley, F.A.C.P., Claremont, Calif.—1 reprint;
Dr. Wesley Wayne Lake (Associate), Pass Christian, Miss.—1 reprint;
Dr. Benjamin Markowitz (Associate), Bloomington, Ill.—2 reprints;
Dr. Aaron E. Parsonnet, F.A.C.P., Newark, N. J.—2 reprints;
Dr. Kenneth Phillips, F.A.C.P., Miami, Fla.—2 reprints;
Dr. Norman Reider, F.A.C.P., Los Angeles, Calif.—1 reprint;
Dr. Harvey H. Seiple (Associate), Lancaster, Pa.—1 reprint;
Dr. Isaac J. Silverman, F.A.C.P., Washington, D. C.—3 reprints;
Dr. Edwin Eugene Ziegler, F.A.C.P., Boston, Mass.—2 reprints.

In addition to the above gifts, acknowledgment is also made of the donation by Dr. William S. Hubbard, F.A.C.P., Philadelphia, Pa., of a copy of "The People's Medical Lighthouse" by Harmon Knox Root, M.D., published in 1856.

Regional Meeting—Kentucky A. C. P. Members

On December 7, 1940, the Kentucky Fellows and Associates of the American College of Physicians held their annual regional meeting at the Good Samaritan Hospital, Lexington, under the Governorship of Dr. Chauncey W. Dowden, with Dr. John Harvey in charge of arrangements. The clinical program consisted of the following presentations:

"Probable Echinococcus Cyst of the Lung"—Dr. E. J. Murray, Lexington, Ky.
"Actinomycosis of the Jaw"—Dr. Carl W. Fortune, Lexington, Ky.
"Two Unusual Cases of Lung Disease"—Dr. Thornton Scott, Lexington, Ky. (by invitation).

Dr. James D. Bruce, President of the College, Ann Arbor, Mich., was to be the guest of honor and give an address on "Fatigue as a Symptom," but was unable to be present because of illness. Dr. Ernest B. Bradley, who was to conduct a Clinico-Pathological Conference, was also unable to be present because of illness.

In the evening a dinner was held at the Lexington Country Club. Attendance at the meeting was remarkably good, there being forty-three members present. Next year the regional meeting will be held in Louisville.

Among those who spoke at a meeting of the Chicago Society of Internal Medicine on November 25, 1940, were:

Dr. Willard O. Thompson, F.A.C.P., Chicago, Ill.—"Persistence and Recurrence of Toxic Goiter Following Subtotal Thyroidectomy";

Dr. Raphael Isaacs, F.A.C.P., Ann Arbor, Mich.—"Red Blood Cell Size as an Aid in Diagnosis, Prognosis and Treatment";

Dr. Italo F. Volini, F.A.C.P., Chicago, Ill.—"Sulfathiazole in the Treatment of Pneumococcus Pneumonia with a Comparative Study Utilizing Sulfapyridine Therapy" and "Cutaneous and Conjunctival Manifestations of Sulfathiazole Intoxication."

Dr. Edwin E. Osgood, F.A.C.P., Portland, Ore., spoke on "Chemotherapy of Staphylococcus Infections" at the 10th annual meeting of the American Academy of Pediatrics held in Memphis, Tenn., November 18–20, 1940.

The Southwestern Medical Association held its annual meeting and clinical conference in Tucson, Ariz., November 21–23, 1940, under the presidency of Dr. Orville E. Egbert, F.A.C.P., El Paso, Texas. One of the guest speakers at this meeting was Dr. Thomas T. Mackie, F.A.C.P., New York, N. Y.

Dr. Albert M. Snell, F.A.C.P., Rochester, Minn., addressed the Evanston Branch of the Chicago Medical Society, November 7, 1940, on "Recent Studies on Deficiency States and Vitamin Therapy."

Among the speakers at a special meeting of the New England Heart Association in Boston, Mass., November 8, 1940, to honor the late Dr. Maude E. S. Abbott, formerly Assistant Professor of Medical Research and Curator of the medical museum, McGill University Faculty of Medicine, Montreal, were:

Dr. Charles F. Martin, M.A.C.P., Montreal, Que.—"Dr. Abbott and McGill University";

Dr. Paul D. White, F.A.C.P., Boston, Mass.—"Her Contribution to Cardiology";

Dr. Emanuel Libman, F.A.C.P., New York, N. Y.—"Personal Reminiscences."

On November 19, 1940, Lt. Col. Arthur Parker Hitchens, F.A.C.P., (MC), U.S.A., Philadelphia, Pa., spoke on "History and Biology of the Anthrax Bacillus" and Dr. Henry Field Smyth, F.A.C.P., Philadelphia, Pa., spoke on "Anthrax in the United States" at a symposium on anthrax sponsored by the Bureau of Industrial Hygiene of the Pennsylvania Department of Health and the Philadelphia Department of Health.

Dr. Russell L. Haden, F.A.C.P., Cleveland, Ohio, spoke on "Treatment of Anemia" and Dr. David C. Wilson, F.A.C.P., Charlottesville, Va., spoke on "New Drugs in Neuropsychiatry" at a meeting of the Southwestern Virginia Medical Society in Marion, Va., October 2, 1940.

Dr. George Fordham, F.A.C.P., Powellton, W. Va., spoke on "Developing a Medical Program for a Coal Industry" at a meeting of the Clinch Valley Medical Society held in Norton, Va., October 18, 1940.

The 3rd annual meeting of the American Academy of Dermatology and Syphilology was held in Chicago, Ill., December 8–11, 1940. Among the guest speakers at this meeting were:

Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich.—"Diseases of the Blood and Blood Forming Organs: Their Relation to the Skin and Mucous Membrane";

Dr. Elmer L. Sevringhaus, F.A.C.P., Madison, Wis.—"Endocrines and Their Relation to Dermatology."

Dr. Udo J. Wile, F.A.C.P., Ann Arbor, Mich., conducted a symposium on syphilis at this meeting.

At the annual meeting of the National Foundation for Infantile Paralysis, November 7–8, 1940, held in New York, N. Y., Dr. Herman N. Bundesen, F.A.C.P., Chicago, Ill., was elected Chairman of the Committee on Public Health (Epidemics). Dr. Bundesen succeeds Dr. Thomas Parran, F.A.C.P., Surgeon General of the U. S. Public Health Service, Washington, D. C., who resigned. Dr. James S. McLester, F.A.C.P., Birmingham, Ala., was reëlected Chairman of the Committee on Nutritional Research of the Foundation.

The National Institute of Health has formed a new unit for the study of problems of aging, the Unit on Gerontology. This Unit announces that it is conducting a survey of the present trends of active and contemplated investigations in this field. The Unit feels that the analysis of the information elicited by this survey will facilitate closer coöperation among investigators interested in related problems, will emphasize the urgent need for augmented support of studies for the problems of senescence, and will be an invaluable aid in formulating future research programs.

Dr. Edward J. Stieglitz, F.A.C.P., Garrett Park, Md., is in charge of the investigations in gerontology. Dr. Anton J. Carlson, F.A.C.P., Chicago, Ill., and Dr. William D. Stroud, F.A.C.P., Philadelphia, Pa., are among those who have been appointed to the National Advisory Committee.

Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn., discussed "Functional Gastrointestinal Disorders" at a meeting of the Peoria (Ill.) Medical Society on November 12, 1940.

Dr. Jay Arthur Myers, F.A.C.P., Minneapolis, Minn., spoke on "The Control of Tuberculosis" at a meeting of the Fort Wayne Medical Society in Fort Wayne, Ind., October 15, 1940.

Dr. Daniel L. Sexton, F.A.C.P., St. Louis, Mo., spoke on "Endocrine Treatment in General Practice" at a meeting of the Gibson County Medical Society in Princeton, Ind., October 14, 1940.

At a meeting of the Wyandotte County Medical Society in Kansas City, Kan., November 5, 1940, Dr. Henry M. Winans, F.A.C.P., Dallas, Texas, discussed "Anemia—Diagnosis of Difficult Cases."

At a recent meeting of the section on surgery of the Buffalo (N. Y.) Academy of Medicine, Dr. J. Arnold Bargen, F.A.C.P., Rochester, Minn., spoke on "Differentiation Between Various Types of Ulcerative Colitis and Their Management."

Dr. Henry L. Bockus, F.A.C.P., Philadelphia, Pa., was the speaker at the autumn postgraduate series of lectures sponsored by the Mahoning County Medical Society in

Youngstown, Ohio, November 14–15, 1940. The subjects of his lectures were: "Present Clinical Status of Chronic Gastritis"; "What Constitutes Adequate Therapy for Chronic Peptic Ulcer"; "Practical Application of Recent Advances in Our Knowledge of Liver Functions"; "Diagnosis and Management of Chronic Ileitis and Ileocolitis"; and "Diagnosis and Management of the 'Irritable Colon.'"

The 9th annual clinical meeting of the Postgraduate Medical Assembly of South Texas was held in Houston, Texas, December 3–5, 1940. Among the guest speakers at this Assembly were the following: Dr. Horton R. Casparis, F.A.C.P., Nashville, Tenn.; Dr. Milton B. Cohen, F.A.C.P., Cleveland, Ohio; Dr. Byrl R. Kirklin, F.A.C.P., Rochester, Minn.; Dr. Henry K. Mohler, F.A.C.P., Philadelphia, Pa.; and Dr. George Morris Piersol, F.A.C.P., Philadelphia, Pa.

Dr. David A. Tucker, Jr., F.A.C.P., Cincinnati, Ohio, spoke on "Daniel Drake, Pioneer Medical Educator of the Middle West" and Dr. Logan Clendening, F.A.C.P., Kansas City, Mo., spoke on "Memorials of Medicine in America" at the fall meeting of the American Association of the History of Medicine, held in Cleveland, Ohio, October 7, 1940.

On November 20, 1940, Dr. Emanuel Libman, F.A.C.P., New York, N. Y., delivered the third annual Louis Gross Memorial Lecture at the Montreal Jewish General Hospital, under the auspices of the Montreal (Can.) Clinical Society. The subject of his lecture was "Endocarditis and 'Libman-Sachs' Disease.'"

Dr. Francis M. Pottenger, F.A.C.P., Monrovia, Calif., spoke on "Physiologic Approach to Disease" and "The Place of the General Practitioner in the Tuberculosis Program of the Future" at two of the scientific sessions of the Annual Fall Conference of the Oklahoma City Clinical Society held in Oklahoma City, Okla., October 28–31, 1940. Dr. Pottenger was also the principal speaker at the annual banquet of this Society. He spoke on "Can Democracy Be Preserved?"

The 2nd Annual Meeting of the Pennsylvania Psychiatric Society was held in Philadelphia, Pa., October 3, 1940. Among the speakers at this meeting were the following:

Dr. Samuel B. Hadden, F.A.C.P., Philadelphia, Pa.—"Treatment of the Neuroses by Class Technic";

Dr. Lauren H. Smith, F.A.C.P., Philadelphia, Pa.—"First Impressions of Electroshock Treatment in the Psychoses";

Dr. Howard K. Petry (Associate), Harrisburg, Pa.—"Mental Hygiene."

At this meeting Dr. Henry I. Klopp, F.A.C.P., Allentown, Pa., was elected President and Dr. Baldwin L. Keyes, F.A.C.P., Philadelphia, Pa., President-Elect. Dr. William W. Richardson, F.A.C.P., Mercer, Pa., was elected one of the Councillors, and Dr. George J. Wright, F.A.C.P., Pittsburgh, Pa., was elected one of the Auditors.

Dr. Paul H. Ringer, F.A.C.P., Asheville, N. C., was elected President of the Southern Medical Association at its recent meeting in Louisville, Ky.

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., presented an exhibit on "Deficiency Disease with Special Reference to Diagnosis and Treatment" at the Assembly of the Inter-state Post Graduate Medical Association of North America held in Cleveland, Ohio, October 14–18, 1940.

Dr. Kelly also presented a paper on "The Present Status of Deficiency Disease with Special Reference to Vitamin Therapy" before the Burlington County Medical Society at Moorestown, N. J., on November 14, 1940.

Dr. Mark Gerstle, Jr., F.A.C.P., has been assigned to active duty at the U. S. Naval Training Station, San Diego, Calif. Dr. Gerstle holds the rank of Lieutenant in the Medical Corps of the U. S. Naval Reserve.

Dr. Rufus S. Reeves, F.A.C.P., Philadelphia, Pa., was the guest speaker at a meeting of the Hartford (Conn.) Medical Society, November 18, 1940. Dr. Reeves spoke on "Graduate Medical Education."

Dr. Harold J. Harris (Associate), Westport, N. Y., gave a radio address over station WNYC on the subject of brucellosis, under the auspices of the New York Academy of Medicine, December 12, 1940.

On December 16, 1940, the Northern Medical Association of Philadelphia held its regular meeting. Among those who spoke at this meeting were:

Dr. Harold L. Goldburgh, F.A.C.P., Philadelphia, Pa.—"Weil's Disease—Prevalence and Diagnosis";

Dr. Hyman I. Goldstein (Associate), Camden, N. J.—"Story of Ulcer of the Stomach and Duodenum."

Dr. Dan G. Stine, F.A.C.P., Columbia, Mo., was named President-Elect of the Mississippi Valley Medical Society at the recent annual meeting on November 17, 1940, of the Board of Directors. Dr. Harold Swanberg, F.A.C.P., Quincy, Ill., was reëlected Secretary-Treasurer. Among those elected to the Board of Directors of this Society were Dr. E. Sanborn Smith, F.A.C.P., Kirksville, Mo., and Dr. George B. Lake (Associate), Waukegan, Ill.

The 3rd Annual Congress on Industrial Health sponsored by the Council on Industrial Health of the American Medical Association was held in Chicago, Ill., January 13–14, 1941. Dr. Edward J. Stieglitz, F.A.C.P., Bethesda, Md., spoke on "Aging as a Problem of Industrial Health," and Dr. George Morris Piersol, F.A.C.P., Philadelphia, Pa., spoke on "The Rôle of the Physician in Industry in the Control of Acute Respiratory Disease." Dr. Francis E. Senear, F.A.C.P., Chicago, Ill., presided at a clinic and symposium on "Industrial Dermatosis."

Dr. Hyman I. Goldstein (Associate), Camden, N. J., was elected President of the New Jersey Gastro-enterological Society, a chapter of the National Gastro-enterological Association, at the December meeting of the Society held in Newark, N. J. Among those elected to the Executive Board of this Society were Dr. Manfred Kraemer, F.A.C.P., Newark, N. J., and Dr. Sigurd W. Johnsen, F.A.C.P., Passaic, N. J.

Dr. Lyle Motley, F.A.C.P., Memphis, Tenn., spoke on "Indication and Uses of Sulfanilamide, Sulfapyridine, Sulfathiazole" at the meeting of the Third Councilor District Medical Society in Helena, Ark., October 24, 1940.

Dr. Harold Swanberg, F.A.C.P., Quincy, Ill., who is Secretary of the Mississippi Valley Medical Society, has announced that the Society offers annually a cash prize of $100.00, a gold medal, and a certificate of award for the best unpublished essay

on any subject of general medical interest (including medical economics) and practical value to the general practitioner of medicine. Certificates of merit may also be granted to the physicians whose essays are rated second and third best. Contestants must be members of the American Medical Association who are residents of the United States. The winner will be invited to present his contribution before the next annual meeting of the Mississippi Valley Medical Society at Cedar Rapids, Iowa, October 1–3, 1941, the Society reserving the exclusive right to first publish the essay in its official publication—the *Mississippi Valley Medical Journal*. Contributions shall not exceed 5000 words, be typewritten in English in manuscript form, submitted in five copies and be received not later than May 1, 1941.

Dr. Jacob C. Geiger, F.A.C.P., Director of Public Health, City and County of San Francisco, Calif., has received the following citation from the Consulate General of Mexico: "I have the honor and high personal privilege to inform you that I have been designated by the Secretary of Foreign Affairs of the Government of Mexico to express to you the official recognition by the Mexican Government of your distinguished services in your field, and to convey to you its gratitude and appreciation of your work."

Dr. William M. Ballinger, F.A.C.P., Washington, D. C., has been made Associate Professor of Gastro-enterology at the Georgetown University School of Medicine, Washington, D. C.

Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill., recently spoke on "Relation of Physiology to Modern Medicine" at a joint meeting of the Des Moines Academy of Medicine and the Polk County Medical Society in Des Moines, Iowa.

Among the speakers at a symposium on chemotherapy presented by the Long Island College of Medicine, New York, N. Y., were the following:

Dr. Yale Kneeland, Jr. (Associate), Assistant Professor of Medicine, Columbia University College of Physicians and Surgeons—"The Sulfonamides in Pneumonia";
Dr. Josephine B. Neal, F.A.C.P., Clinical Professor of Neurology, Columbia University College of Physicians and Surgeons—"The Sulfonamides in Meningitis";
Dr. Elliston Farrell (Associate), Assistant Clinical Professor of Medicine, Long Island College of Medicine—"Toxic Reactions."

Dr. David C. Wilson, F.A.C.P., Charlottesville, Va., was elected President of the Mental Hygiene Society of Virginia at the annual meeting in Richmond, October 31, 1940.

Dr. Lawrence Kolb, F.A.C.P., Washington, D. C., was one of the guest speakers at this meeting. Dr. Kolb discussed treatment and research in the field of mental disease.

Dr. Chester S. Keefer, F.A.C.P., Boston, Mass., spoke on "The Present Status of Chemotherapy in the Treatment of Infectious Diseases" at the annual meeting of the Association of Life Insurance Medical Directors in Boston, October 16–18, 1940.

Dr. James K. Hall (Associate), Richmond, Va., was elected Vice President of the Southern Psychiatric Association at its recent annual meeting held in Jacksonville, Fla.

Dr. Henry Mason Smith, F.A.C.P., Tampa, Fla., spoke on "The Psychological and Economic Influence of Alcohol" at this meeting.

At the 19th annual meeting of the Central Neuropsychiatric Association held in Milwaukee, Wis., October 25–26, 1940, Dr. William C. Menninger, F.A.C.P., Topeka, Kan., was reëlected Secretary. Dr. Theodore L. Squier, F.A.C.P., Milwaukee, Wis., spoke on "Emotional Factors in Allergic States," Dr. Andrew I. Rosenberger, F.A.C.P., Milwaukee, Wis., spoke on "Observations on Treatment of Amyotrophic Lateral Schlerosis (Leukopoliomyelopathy) with Vitamin E," and Dr. Carroll W. Osgood, F.A.C.P., Wauwatosa, Wis., presented a symposium on shock therapy.

Dr. James J. Waring, F.A.C.P., Denver, Colo., was elected President of the American Clinical and Climatological Association at its annual meeting in White Sulphur Springs, W. Va., October 28–30, 1940. Dr. Benjamin M. Baker, Jr., F.A.C.P., Baltimore, Md., and Dr. Frank A. Evans, F.A.C.P., Pittsburgh, Pa., were elected Vice Presidents of this society.

Among those who spoke at this meeting were the following:

Dr. Paul D. White, F.A.C.P., Boston, Mass.—"Coronary Thrombosis—Ten Years Later";

Dr. Robert L. Levy, F.A.C.P., New York, N. Y.—"Relief of Anginal Pain by Paravertebral Alcohol Block: A Summary of Ten Years' Experience";

Dr. F. Janney Smith, F.A.C.P., Detroit, Mich.—"Kidney Complications of the Chemotherapy of Pneumonia";

Dr. Frederic M. Hanes, F.A.C.P., Durham, N. C.—"The Therapy of Deficiency States."

Dr. Charles W. Mills, F.A.C.P., and Dr. Orin Jocevious Farness (Associate), Tucson, Ariz.—"Coccidioides Immitis Infection in Southern Arizona";

Dr. Truman G. Schnabel, F.A.C.P., and Dr. Ferdinand Fetter, F.A.C.P., Philadelphia, Pa.—"Fever Therapy in Rheumatoid Arthritis."

The Collier Trophy, awarded annually for the greatest achievement in aviation in America and one of the most important national awards in aviation, was recently presented to Captain Harry G. Armstrong (Associate), (MC), U. S. A., and Dr. Walter M. Boothby, F.A.C.P., Rochester, Minn. Presentation of this trophy was made by President Roosevelt on behalf of the National Aeronautic Association and was presented to the physicians for "their contribution to the safety record by their work in the field of aviation medicine generally and pilot fatigue in particular."

Dr. Fred W. Wilkerson, F.A.C.P., Montgomery, Ala., spoke on "Cardiac Neuroses" at a recent meeting of the Northwestern Division of the Medical Association of the State of Alabama held in Reform, Ala.

On November 19, 1940, Dr. Virgil P. Sydenstricker, F.A.C.P., Augusta, Ga., gave one of the De Lamar Lectures sponsored by the Johns Hopkins University School of Hygiene and Public Health. The subject of his lecture was "Dietary Problems of the Southern United States."

Dr. August A. Werner, F.A.C.P., St. Louis, Mo., delivered on November 27, 1940, the first Max Ballin Lecture, sponsored by the North End Clinic of Detroit, Mich., on "Recent Advances in Endocrine Therapy." On December 4, 1940, Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn., gave the second lecture of this series. Dr.

Alvarez spoke on "Recent Advances in Treatment of Food Allergy." The third lecture was given December 11, 1940, by Dr. Harold J. Jeghers (Associate), Boston, Mass. Dr. Jeghers spoke on "Recent Advances in Vitamin Therapy."

The 37th annual meeting of the Puerto Rico Medical Association was held in Santurce, P. R., December 12–15, 1940, under the presidency of Dr. Oscar G. Costa-Mandry, F.A.C.P., San Juan, P. R. Among the speakers at this meeting were the following:

Dr. Louis F. Bishop, F.A.C.P., New York, N. Y.—"Coronary Disease—Its Diagnosis and Treatment";

Dr. Malcolm T. MacEachern, F.A.C.P., Chicago, Ill.—"Trends in Specialization in Medicine";

Dr. Ramon M. Suarez, F.A.C.P., and Dr. Enrique Koppisch, F.A.C.P., San Juan, P. R.—"Weil's Disease in Puerto Rico."

Dr. Ralph C. Matson, who is Chairman of the Committee for the Advancement of Scientific Programs in Organized Medicine, of the American College of Chest Physicians, organized and conducted a postgraduate course in diseases of the chest. The course was given under the auspices of the University of Oregon Medical School and the Pacific Northwest section of the American College of Chest Physicians, comprised of Fellows of the College residing in Oregon, Washington, Idaho and Montana. Sixty-seven doctors from this area attended the meeting, which was a two-day session given on December 13 and 14, 1940.

Dr. C. F. De Garis, F.A.C.P., Professor of Anatomy at the University of Oklahoma School of Medicine, has been awarded the A. Cressy Morrison Prize in Natural Science for 1940 by the New York Academy of Sciences for a paper entitled, "The Aortic Arch in Primates." This paper reports the patterns of branches of the aortic arch in a large collection, each family of the Order Primates being represented. The relation of thorax shape to aortic branching is a point of special inquiry. The same type of study, using the same material, will be extended to the heart and lungs.

It is said the strength of this paper rests mainly on the abundant material, most of which was acquired by the author during his stay at the Johns Hopkins University Medical School, 1925–36. The Prize was accompanied by an award of $200.00.

Western Reserve University has recently announced a grant from Commodore Louis D. Beaumont, formerly of Cleveland, now residing in Florida, of $8,500.00 to continue the research in hypertension being carried on by Dr. Harry Goldblatt, Professor and Associate Director of the Institute of Pathology and the recipient of the John Phillips Memorial Award by the American College of Physicians in 1938.

New Elections to College Membership

At a meeting of the Board of Regents December 15, 1940, at the headquarters building, Philadelphia, the following candidates were regularly elected to the class indicated:

Elections to Fellowship

December 15, 1940

Fellowship Candidates	*Sponsors*
Alabama	
Maurice James Abrams, Brewton	J. Harold Watkins, James F. Alison, Fred Wilkerson
James Owen Finney, Gadsden	James S. McLester, John B. Youmans, Fred Wilkerson

Fellowship Candidates	*Sponsors*
ARKANSAS	
Paul Chadbourne Eschweiler, Little Rock	Frank Bethel Cross, Edwin P. Maynard, Jr., C. F. Tenney, Oliver C. Melson
CALIFORNIA	
Clarence Wilmott Olsen, Los Angeles	Newton Evans, R. Manning Clarke, James F. Churchill
Leslie Hall Redelings, San Diego	R. H. Sundberg, William C. Cooke, James F. Churchill
John Carl Schlappi, San Diego	Stacy R. Mettier, Dudley W. Bennett, James F. Churchill
Rufus Anton Schneiders, San Diego	Lyell C. Kinney, R. H. Sundberg, James F. Churchill
COLORADO	
Henry Wendell Maly, Colorado Springs	John A. Sevier, A. Lee Briskman, James J. Waring
Maurice Katzman, Denver	James R. Arneill, John G. Ryan, James J. Waring
CONNECTICUT	
Walls Willard Bunnell, Farmington	John A. Wentworth, James E. Hutchison, Charles H. Turkington
William Harry Resnik, Stamford	Chester S. Keefer, Augustus R. Felty, Charles H. Turkington
John S. Staneslow, Waterbury	John H. Foster, Arthur H. Jackson, Charles H. Turkington
DISTRICT OF COLUMBIA	
Donald William Ingham, Washington	William P. Argy, Michael J. McInerney, Wallace M. Yater
MEDICAL CORPS, U. S. ARMY	
J. Vincent Falisi, Fort Sill, Okla.	James C. Magee
Robert E. Thomas, Schofield Barracks, T. H.	James C. Magee
MEDICAL CORPS, U. S. NAVY	
Walter Johnson Pennell, Washington, D. C.	Joel J. White, William W. Hargrave, Ross T. McIntire
U. S. PUBLIC HEALTH SERVICE	
Thomas Haze Tomlinson, Jr., Washington, D. C.	Lawrence Kolb, Thomas Parran
FLORIDA	
Robert Johnson Needles, St. Petersburg	James A. Bradley, Roscoe H. Knowlton, T. Z. Cason
William Glenn Post, Jr., St. Petersburg	Roscoe H. Knowlton, Arnold S. Anderson, T. Z. Cason
GEORGIA	
Evert Abram Bancker, Atlanta	Trimble Johnson, Hal M. Davison, Glenville Giddings
Joseph Carey Massee, Atlanta	C. W. Strickler, Trimble Johnson, Glenville Giddings
Cyrus Warren Strickler, Jr., Atlanta	Russell H. Oppenheimer, J. G. Bachmann, Glenville Giddings
Martin Van Buren Teem, Marietta	Carter Smith, T. S. Claiborne, Glenville Giddings

Fellowship Candidates	*Sponsors*
ILLINOIS	
Clarence Lucas Gardner, Jr., Aurora	Walter L. Palmer, Vernon L. Evans, LeRoy H. Sloan
William Samuel Hoffman, Chicago	Willard O. Thompson, A. C. Ivy, James G. Carr, LeRoy H. Sloan
Clarence James McMullen, Chicago	L. C. Gatewood, James G. Carr, LeRoy H. Sloan
Samuel Glenwood Plice, Chicago	James G. Carr, Italo F. Volini, LeRoy H. Sloan
Hugo Rohonyi Rony, Chicago	A. C. Ivy, Lowell D. Snorf, LeRoy H. Sloan
Harry Allen Richter, Evanston	Lowell D. Snorf, James G. Carr, LeRoy H. Sloan
IOWA	
Fred Sternagel, West Des Moines	John H. Peck, Walter L. Bierring, Fred M. Smith
KANSAS	
Norman Reider, Topeka	William C. Menninger, Philip W. Morgan, Thomas T. Holt
LOUISIANA	
Robert Hebard Bayley, New Orleans	Edgar Hull, Louis A. Monte, J. E. Knighton
James Kirby Howles, New Orleans	Clyde Brooks, J. H. Musser, J. E. Knighton
Carl John Walfrid, New Orleans	Stewart E. Doolittle, Nils P. Larsen, H. L. Arnold, J. E. Knighton
MASSACHUSETTS	
Curtis Tuttle Prout, Arlington Heights	Frank N. Allan, Elmer C. Bartels, William B. Breed
Walter Swan Burrage, Boston	Robert S. Palmer, Francis M. Rackemann, William B. Breed
Frank Pray Foster, Boston	Frank N. Allan, E. V. Allen, Reginald Fitz, William B. Breed
Thomas Van Orden Urmy, Boston	F. Dennette Adams, J. H. Means, William B. Breed
J. Victor Breen, Pittsfield	James Z. Naurison, Paul D. White, William B. Breed
Ira Milburn Dixson, Stockbridge	Horace K. Richardson, Warfield T. Longcope, William B. Breed
Robert Battaile Hiden, Stockbridge	Horace K. Richardson, Walter Bauer, William B. Breed
MICHIGAN	
Charles Fremont McKhann, Ann Arbor	Herman H. Riecker, Frank N. Wilson, Henry R. Carstens
Louis Harry Newburgh, Ann Arbor	Herman H. Riecker, Cyrus C. Sturgis, Henry R. Carstens
William Edward Jahsman, Ferndale	Robert H. Durham, Frank J. Sladen, Henry R. Carstens
MINNESOTA	
Phillip Hallock, Minneapolis	Jay C. Davis, Henry L. Ulrich, E. V. Allen
Cecil James Watson, Minneapolis	S. Marx White, A. R. Barnes, E. V. Allen
Hugh Roland Butt, Rochester	Albert M. Snell, George B. Eusterman, E. V. Allen
Walter Frederick Kvale, Rochester	Albert M. Snell, James F. Weir, E. V. Allen
MISSOURI	
Robert Emmet Britt, St. Louis	Ralph A. Kinsella, Alphonse McMahon, A. C. Griffith
David Brislin Flavan, St. Louis	Ralph A. Kinsella, Alphonse McMahon, David P. Barr, A. C. Griffith
David Miller Skilling, Jr., St. Louis	Walter Baumgarten, Howard A. Rusk, A. C Griffith

Fellowship Candidates	*Sponsors*
	MONTANA
Wayne Gordon, Billings	Malcolm D. Winter, M. A. Shillington, Ernest D. Hitchcock
	NEBRASKA
Esley Joseph Kirk, Omaha	Lynn T. Hall, Rodney W. Bliss, Warren Thompson
Ernest Lynn MacQuiddy, Omaha	Rodney W. Bliss, Adolph Sachs, Warren Thompson
	NEVADA
George Arthur Cann, Reno	Lawrence Parsons, O. Hovenden, Ernest H. Falconer
	NEW HAMPSHIRE
Charles Henry Parsons, Concord	Fred Ellsworth Clow, Colin C. Stewart, Robert B. Kerr
	NEW JERSEY
George Ginsberg, Hoboken	Herman O. Mosenthal, S. Edward King, George H. Lathrope
	NEW YORK
Aaron Leonard Burger, Brooklyn	Philip I. Nash, Thomas J. Longo, C. F. Tenney
Charles Edward Hamilton, Brooklyn	Henry M. Moses, Frank Bethel Cross, C. F. Tenney
William August Lange, Brooklyn	Alexis T. Mays, Foster Murray, C. F. Tenney
John Gerard Senese, Brooklyn	William H. Lohman, Edwin P. Maynard, Jr., C. F. Tenney
Charles Windwer, Brooklyn	Harry R. Litchfield, Louis Harris, C. F. Tenney
James Patrick Kinney, Buffalo	J. Herbert Donnelly, Thomas J. Walsh, Nelson G. Russell
John Josiah Maisel, Buffalo	Ivan Hekimian, Harvey C. Schneider, Nelson G. Russell
Nelson W. Strohm, Buffalo	Carroll J. Roberts, J. Herbert Donnelly, Nelson G. Russell
Alexander Scott Dowling, Corning	Joseph T. Wearn, J. M. Hayman, Jr., Nelson G. Russell
Alan Ramseur Anderson, Freeport	Irving S. Wright, A. Wilbur Duryee, C. F. Tenney
Stanton Tice Allison, New York	Edward P. Eglee, Grant Thorburn, C. F. Tenney
Morris Block, New York	Mills Sturtevant, Currier McEwen, C. F. Tenney
Norton Sager Brown, New York	Randolph West, Robert F. Loeb, C. F. Tenney
Beeckman J. Delatour, New York	Herman O. Mosenthal, George M. Goodwin, C. F. Tenney
Emanuel Zachary Epstein, New York	Arthur M. Master, Herman Lande, C. F. Tenney
William Travis Gibb, Jr., New York	W. P. Anderton, James Ralph Scott, C. F. Tenney
LeMoyne Copeland Kelly, New York	R. Garfield Snyder, Willard H. Squires, C. F. Tenney
Henry Bingham Kirkland, New York	Asa L. Lincoln, Arthur C. DeGraff, C. F. Tenney
Joseph Kovacs, New York	Irving S. Wright, A. Wilbur Duryee, C. F. Tenney
Julia Valentine Lichtenstein, New York	I. Ogden Woodruff, James Alex. Miller, C. F. Tenney
Victor Wesley Logan, New York	Arthur L. Holland, Howard F. Shattuck, C. F. Tenney
Herbert Pollack, New York	George Baehr, Arthur M. Master, C. F. Tenney
Jacob Segal, New York	Grant Thorburn, J. Burns Amberson, Jr., C. F. Tenney

Fellowship Candidates	*Sponsors*
Israel Steinberg, New York	Mills Sturtevant, Currier McEwen, C. F. Tenney
Arthur Julian Horton, St. Albans	Frank R. Mazzola, Goodwin A. Distler, C. F. Tenney
Herman Tarnower, Scarsdale	J. Burns Amberson, Jr., I. Ogden Woodruff, C. F. Tenney

NORTH CAROLINA

Andrew Blair, Charlotte	E. J. Wannamaker, A. A. Barron, C. H. Cocke
Luther Wrentmore Kelly, Charlotte	E. J. Wannamaker, T. Preston White, C. H. Cocke
Merle Dumont Bonner, Jamestown	Frederick R. Taylor, Philip W. Flagge, C. H. Cocke
James Hubert McNeill, North Wilkesboro	Paul P. McCain, S. M. Bittinger, C. H. Cocke

OKLAHOMA

Homer Albert Ruprecht, Tulsa	Russell C. Pigford, S. C. Shepard, Lea A. Riely

OREGON

Willard Fletcher Hollenbeck, Portland	John H. Fitzgibbon, Ernest L. Boylen, Homer P. Rush

PENNSYLVANIA

William Jefferson Armstrong, Butler	Walter F. Donaldson, C. Sidney Burwell, R. R. Snowden
Robert Sloan Lucas, Butler	Charles W. Morton, Walter M. Bortz, R. R. Snowden
John Wherry Shadle, Butler	Eliah Kaplan, John O. Woods, R. R. Snowden
Thomas Arthur Johnson, Drexel Hill	H. L. Bockus, Joseph T. Beardwood, Edward L. Bortz
Arthur Orr Hecker, Harrisburg	C. E. Ervin, C. P. Faller, Edward L. Bortz
Frank Frederick Dunott Reckord, Harrisburg	Jesse L. Lenker, John B. McAlister, Edward L. Bortz
David Long Perry, New Castle	Eliah Kaplan, Wayne W. Bissell, R. R. Snowden
John Trimble Eads, Philadelphia	Henry K. Mohler, E. J. G. Beardsley, Edward L. Bortz
Joseph Edeiken, Philadelphia	James E. Cottrell, Charles C. Wolferth, Edward L. Bortz
George Elbert Farrar, Jr., Philadelphia	Charles L. Brown, Edward Weiss, Edward L. Bortz
Roy L. Langdon, Philadelphia	Charles L. Brown, Truman G. Schnabel, Edward L. Bortz
John Lansbury, Philadelphia	Leonard G. Rowntree, Charles L. Brown, Edward L. Bortz
Alexander Margolies, Philadelphia	James E. Cottrell, Charles C. Wolferth, Edward L. Bortz
William Urie McClenahan, Philadelphia	T. Grier Miller, Richard A. Kern, Edward L. Bortz
Abraham Trasoff, Philadelphia	Thomas Fitz-Hugh, Jr., Samuel A. Loewenberg, Edward L. Bortz
Francis A. Aaron, Pittsburgh	Walter F. Donaldson, George Booth, R. R. Snowden
George Gregory Burkley, Pittsburgh	H. G. Schleiter, C. Howard Marcy, R. R. Snowden

TENNESSEE

William Ramsey Blue, Memphis	Whitman Rowland, L. C. Sanders, J. O. Manier

Fellowship Candidates	*Sponsors*
Texas	
Lang Floyd Holland, Austin	Raymond Gregory, George M. Decherd, Jr., M. D. Levy
M. Hill Metz, Dallas	D. W. Carter, Jr., W. G. Reddick, M. D. Levy
Joseph Fielding McVeigh, Fort Worth	Will S. Horn, T. C. Terrell, M. D. Levy
Frances Ralston Vanzant, Houston	LeRoy B. Duggan, F. R. Lummis, M. D. Levy
William Walton Bondurant, Jr., San Antonio	Lee Rice, Herbert Hill, M. D. Levy
William Henry Cade, San Antonio	Alvis E. Greer, H. N. Gemoets, M. D. Levy
Vermont	
Christopher Campbell Shaw, Bellows Falls	Dwight L. Siscoe, Howard F. Root, Paul K. French
Virginia	
Oscar Swineford, Jr., Charlottesville	H. B. Mulholland, Eugene M. Landis, Walter B. Martin
Kenneth Dawson Graves, Roanoke	George B. Lawson, J. W. Preston, Walter B. Martin
Collins Denny Nofsinger, Roanoke	Blanton P. Seward, George B. Lawson, Walter B. Martin
Washington	
Thomas Jefferson Fatherree, Soap Lake	Edwin G. Bannick, Robert F. Foster, C. E. Watts
West Virginia	
James Lowrance Wade, Parkersburg	Walter E. Vest, Frank J. Holroyd, Albert H. Hoge
Andrew Currence Woofter, Parkersburg	Walter E. Vest, Frank J. Holroyd, Albert H. Hoge
Puerto Rico	
Jose Nicolas Gandara, Ponce	Manuel de la Pila Iglesias, Enrique Koppisch, Ramon M. Suarez
Dominion of Canada	
British Columbia	
Samuel E. C. Turvey, Vancouver	C. E. Watts, J. M. Blackford, G. F. Strong
New Brunswick	
William Oswald McDonald, St. John	R. J. Collins, A. B. Walter, H. A. Farris
Nova Scotia	
Thomas Alphonsus Lebbetter, Yarmouth	Gerald R. Burns, R. J. Collins, H. A. Farris
Saskatchewan	
Harold Sugarman, Saskatoon	D. M. Baltzan, P. H. Sprague, G. F. Strong

"Resolved, that the following list of 19 be and herewith are elected to Fellowship in the American College of Physicians as of April 20, 1941:"

Massachusetts	
Winthrop Wetherbee, Jr., Boston	James M. Faulkner, Elliott P. Joslin, William B. Breed

Fellowship Candidates	*Sponsors*
New York	
Harry Mandelbaum, Brooklyn	Simon R. Blatteis, Irving J. Sands, C. F. Tenney
Louis Harry Sigler, Brooklyn	Philip I. Nash, Thomas J. Longo, C. F. Tenney
Irving Robert Juster, Glens Falls	Morris Maslon, W. H. Ordway, C. F. Tenney
Franklin Weimer Fry, Hempstead	Louis H. Bauer, Everett C. Jessup, C. F. Tenney
Norman Plummer, New York	Asa L. Lincoln, W. P. Anderton, C. F. Tenney
William Payne Thompson, New York	Franklin M. Hanger, Randolph West, C. F. Tenney
William Hammond, Scarsdale	George W. Cumbler, James R. Scott, C. F. Tenney
Oklahoma	
Vern Hurschel Musick, Oklahoma City	Wann Langston, John E. Heatley, Lea A. Riely
Pennsylvania	
D. Sergeant Pepper, Bala-Cynwyd	Arthur W. Phillips, T. Grier Miller, Edward L. Bortz
Elmer Highberger, Jr., Greensburg	Frank A. Evans, C. C. Wholey, R. R. Snowden
Francis James Braceland, Philadelphia	Kenneth E. Appel, Lauren H. Smith, Edward L. Bortz
Perk Lee Davis, Philadelphia	Wm. Egbert Robertson, Harold W. Jones, Edward L. Bortz
Charles William Dunn, Philadelphia	Joseph T. Beardwood, Jr., H. B. Wilmer, George Morris Piersol, Edward L. Bortz
Harrison Fitzgerald Flippin, Philadelphia	Thomas Fitz-Hugh, Jr., Charles C. Wolferth, Edward L. Bortz
John Fleming Giering, Wilkes-Barre	G. E. Baker, Edward I. Wolfe, Edward L. Bortz
Tennessee	
Carrol Conway Turner, Memphis	Conley H. Sanford, H. F. Crawford, J. O. Manier
Texas	
Dolph Lange Curb, Houston	Edward H. Schwab, William L. Marr, M. D. Levy
Washington	
Kenneth Kyler Sherwood, Seattle	Edwin G. Bannick, Frederick Slyfield, C. E. Watts

Elections to Associateship

December 15, 1940

Associateship Candidates	*Sponsors*
Alabama	
E. Dice Lineberry, Birmingham	James S. McLester, Edgar G. Givhan, Jr., Fred Wilkerson
I. Milton Wise, Mobile	E. S. Sledge, Daniel T. McCall, Fred Wilkerson
Arkansas	
Frank Marvin Adams, Hot Springs National Park	Charles H. Lutterloh, Arthur G. Sullivan, Oliver C. Melson
John Eugene Greutter, Little Rock	Daniel L. Sexton, H. I. Spector, Oliver C. Melson
Jerome Sickles Levy, Little Rock	W. B. Grayson, Charles H. Lutterloh, Oliver C. Melson

Associateship Candidates	*Sponsors*
CALIFORNIA	
Kenelm Winslow Benson, Berkeley	Philip W. Brown, Russell M. Wilder, E. V. Allen, Ernest H. Falconer
Eliot David Sorsky, Fresno	W. E. Richard Schottstaedt, M. H. Nathanson, Ernest H. Falconer
Walter Everett Macpherson, Los Angeles	D. D. Comstock, Newton Evans, James F. Churchill
William Llewellyn Cover, San Bernardino	Wm. S. McCann, Wm. Philip Corr, James F. Churchill
George Frederick Harsh, San Diego	Clair L. Stealy, Lyell C. Kinney, James F. Churchill
William Alma Winn, Springville	W. E. Richard Schottstaedt, Chesley Bush, Ernest H. Falconer
COLORADO	
Marshall Grant Nims, Denver	Clough Turrill Burnett, C. S. Bluemel, James J. Waring
CONNECTICUT	
James Joseph Hennessy, Hartford	Arthur B. Landry, Timothy F. Brewer, Charles H. Turkington
Joseph Mignone, New Haven	Benedict R. Harris, S. J. Goldberg, Charles H. Turkington
William Finkelstein, Waterbury	Orpheus J. Bizzozero, William E. Hill, Charles H. Turkington
DELAWARE	
H. Wendell Gray, Wilmington	Edgar R. Miller, Olin S. Allen, Lewis B. Flinn
DISTRICT OF COLUMBIA	
E. Raymond Fenton, Washington	William D. Tewksbury, Paul F. Dickens, Wallace M. Yater
Charles Robert Lee Halley, Washington	W. A. Bloedorn, William J. Mallory, Wallace M. Yater
John Watkins Trenis, Washington	Cyrus C. Sturgis, Raphael Isaacs, Henry R. Carstens, Wallace M. Yater
U. S. PUBLIC HEALTH SERVICE	
Robert Kent Maddock, Norfolk, Va.	James P. Leake, Thomas Parran
Edgar Warren Norris, Baltimore, Md.	Charles H. Lutterloh, Arthur G. Sullivan, Oliver C. Melson, Thomas Parran
FLORIDA	
Milton Sibley Saslaw, Miami	E. Sterling Nichol, P. B. Welch, T. Z. Cason
Scheffel Hays Wright, Miami	E. Sterling Nichol, P. B. Welch, T. Z. Cason
Julius Ralph Pearson, Miami Beach	E. Sterling Nichol, P. B. Welch, T. Z. Cason
GEORGIA	
Max Mass, Macon	Alvin E. Siegel, W. W. Chrisman, Glenville Giddings
ILLINOIS	
Gertrude Mary Engbring, Chicago	Italo F. Volini, Leo L. Hardt, James G. Carr, LeRoy H. Sloan
Francis Leo Foran, Chicago	Willard O. Thompson, L. C. Gatewood, LeRoy H. Sloan
William Joseph Hagstrom, Chicago	Italo F. Volini, R. A. Black, LeRoy H. Sloan
Robert Charles Levy, Chicago	Sidney A. Portis, Julius H. Hess, LeRoy H. Sloan
George William Stuppy, Chicago	L. C. Gatewood, Willard O. Thompson, LeRoy H. Sloan
Wayne Wetmore Fox, Evanston	Arthur E. Mahle, James G. Carr, LeRoy H. Sloan

Associateship Candidates	*Sponsors*
	INDIANA
George Wyman Willison, Evansville	Herman M. Baker, C. J. Clark, Robert M. Moore
Ralph Arthur Elliott, Gary	Otis B. Nesbit, Hubert M. English, Robert M. Moore
Irvine Heinly Page, Indianapolis	C. J. Clark, John A. MacDonald, Robert M. Moore
	IOWA
Lawrence James Halpin, Cedar Rapids	Benjamin F. Wolverton, J. Stuart McQuiston, Fred M. Smith
	KANSAS
Mahlon Henry Delp, Kansas City	Fred E. Angle, W. H. Algie, Thomas T. Holt
Don Carlos Peete, Kansas City	Fred E. Angle, W. H. Algie, Thomas T. Holt
Ralph Irving Canuteson, Lawrence	Fred E. Angle, Edw. H. Hashinger, Thomas T. Holt
	KENTUCKY
Foster Douglas Coleman, Louisville	Sam A. Overstreet, John Walker Moore, C. W. Dowden
	LOUISIANA
Thomas Houston Pargen, Jackson	Cecil O. Lorio, Philip H. Jones, J. E. Knighton
Sydney Jacobs, New Orleans	J. H. Musser, J. L. Wilson, J. E. Knighton
Edward de Saunhac Matthews, New Orleans	J. H. Musser, Grace A. Goldsmith, J. E. Knighton
Samuel Bernard Nadler, New Orleans	Randolph Lyons, J. H. Musser, J. E. Knighton
Adolph Thompson Ogaard, New Orleans	O. J. LaBarge, J. H. Musser, J. E. Knighton
Jack Otway Watkins Rash, New Orleans	J. H. Musser, O. J. LaBarge, J. E. Knighton
N. Judson Bender, Shreveport	Arthur A. Herold, M. D. Hargrove, J. E. Knighton
Morgan Whitsitt Matthews, Shreveport	T. P. Lloyd, C. P. Rutledge, J. E. Knighton
Thomas Bell Tooke, Jr., Shreveport	Russell M. Wilder, E. J. Kepler, E. V. Allen, J. E. Knighton
	MARYLAND
Nathan Bernard Herman, Baltimore	Wetherbee Fort, David Tenner, Louis Krause
	MASSACHUSETTS
Stuart Needham Gardner, Salem	Reginald Fitz, Paul D. White, William B. Breed
James Graham Bruce, Springfield	George L. Steele, Theodore S. Bacon, William B. Breed
Max Millman, Springfield	James Z. Naurison, Laurence D. Chapin, William B. Breed
	MICHIGAN
Jerome W. Conn, Ann Arbor	Cyrus C. Sturgis, Arthur C. Curtis, Henry R. Carstens
Richard Harold Freyberg, Ann Arbor	Cyrus C. Sturgis, Frank N. Wilson, Henry R. Carstens
Carl Burritt Beeman, Grand Rapids	Joseph B. Whinery, H. C. Robinson, Henry R. Carstens
J. Heinz Ahronheim, Jackson	A. M. Shaeffer, C. Corley, Henry R. Carstens
Martin Patmos, Kalamazoo	John B. Jackson, Leo E. Westcott, Henry R. Carstens
Josef Samuel Rozan, Lansing	Theodore I. Bauer, Milton Shaw, Henry R. Carstens

Associateship Candidates	*Sponsors*
MINNESOTA	
Francis Edward McDonough, Rochester	Albert M. Snell, James F. Weir, E. V. Allen
George Fredrick Schmitt, Jr., Rochester	Albert M. Snell, Philip S. Hench, E. V. Allen
Donald Maclean Willson, Rochester	Russell M. Wilder, E. J. Kepler, E. V. Allen
MISSOURI	
Russell Waite Kerr, Kansas City	Paul F. Stookey, Harry L. Jones, A. C. Griffith
Orval Raymond Withers, Kansas City	Arthur Graham Asher, Jess Vardeman Bell, A. C. Griffith
Joseph Castro Edwards, St. Louis	Sim F. Beam, Edward W. Cannady, A. C. Griffith
Cyril Mitchell MacBryde, St. Louis	H. L. Alexander, Louis H. Behrens, A. C. Griffith
MONTANA	
Robert William Currie, Billings	Malcolm D. Winter, M. A. Shillington, Ernest D. Hitchcock
NEW JERSEY	
Sloan Giffin Stewart, Atlantic City	Clarence L. Andrews, Hilton S. Read, George H. Lathrope
Emil Henry Grieco, Bayonne	B. S. Pollak, Abraham E. Jaffin, George H. Lathrope
Nathan Schaffer, East Orange	Aaron E. Parsonnet, Manfred Kraemer, George H. Lathrope
Crawford Norbert Baganz, Lyons	Dean H. Duncan, Christopher C. Beling, George H. Lathrope
Irving Loren Applebaum, Newark	Aaron E. Parsonnet, Asher Yaguda, George H. Lathrope
John Eugene Barrett, Newark	Edward C. Klein, Jr., Joseph William Gardam, George H. Lathrope
Edward Valentine Sexton, Teaneck	Paul A. Kennedy, G. Milton Knowles, George H. Lathrope
A. Albert Carabelli, Trenton	Johannes F. Pessel, Richard T. Ellison, George H. Lathrope
NEW YORK	
Irving Ershler, Binghamton	Ronald L. Hamilton, C. H. Berlinghof, Nelson G. Russell
Nagla Mary Laf Loofy, Brooklyn	William H. Lohman, Edwin P. Maynard, Jr., C. F. Tenney
Maurice Morrison, Brooklyn	Irving J. Sands, Simon R. Blatteis, C. E. Tenney
Nathaniel Edwin Reich, Brooklyn	Carl H. Greene, J. Hamilton Crawford, C. F. Tenney
Alexander Solomon Wiener, Brooklyn	Irving J. Sands, Simon R. Blatteis, C. F. Tenney
Edward Francis Driscoll, Buffalo	A. H. Aaron, Francis D. Leopold, Nelson G. Russell
John McAlpine Galbraith, Glen Cove	Everett C. Jessup, William H. Lohman, C. F. Tenney
Jacob Charles Zillhardt, Johnson City	R. J. Wharton, Henry A. Christian, Nelson G. Russell
Wayne Louette Henning, Lake Kushaqua	J. N. Hayes, E. S. McSweeney, Nelson G. Russell, C. F. Tenney
Alexander Altschul, New York	B. P. Stivelman, John L. Kantor, C. F. Tenney
Murray Benson, New York	Leonard G. Weber, Robert L. Hutton, C. F. Tenney
Reginald Conklin, New York	F. Warner Bishop, James Ralph Scott, C. F. Tenney
Meyer Friedenson, New York	John L. Kantor, Arthur M. Master, C. F. Tenney
Abner M. Fuchs, New York	F. Howard Westcott, W. C. Spain, C. F. Tenney

Associateship Candidates	*Sponsors*
M. Leonard Gottlieb, New York	Maximilian A. Ramirez, Henry A. Rafsky, C. F. Tenney
Saul Wallenstein Jarcho, New York	George Baehr, Robert F. Loeb, C. F. Tenney
Sidney Leibowitz, New York	I. W. Held, Wm. Goldring, C. F. Tenney
Louis Rosenbaum, New York	Herbert R. Edwards, B. P. Stivelman, C. F. Tenney
Robert Folger Solley, New York	James Ralph Scott, George M. Goodwin, C. F. Tenney
Morris Tannenbaum, New York	Herbert R. Edwards, Theresa Scanlan, C. F. Tenney
Harry Weiss, New York	B. S. Oppenheimer, John L. Kantor, C. F. Tenney
Harry Louis Segal, Rochester	David B. Jewett, Wm. S. McCann, Nelson G. Russell
Stewart Hayner Jones, Troy	Crawford R. Green, Alson J. Hull, C. F. Tenney
North Carolina	
C. Graham Reid, Charlotte	Paul P. McCain, T. Grier Miller, C. H. Cocke
Karl Shepard, High Point	Frederick R. Taylor, Philip W. Flagge, C. H. Cocke
Hillis Ledbetter Seay, Huntersville	E. J. Wannamaker, T. Preston White, C. H. Cocke
Frank Trumbo Harper, Sanatorium	Paul P. McCain, Paul F. Whitaker, C. H. Cocke
Robert Page Morehead, Wake Forest	Paul F. Whitaker, C. C. Carpenter, C. H. Cocke
North Dakota	
Reinhold O. Goehl, Grand Forks	F. A. Willius, E. L. Tuohy, J. O. Arnson
Ohio	
Frank Theodore Moore, Akron	Clarence L. Hyde, Don B. Lowe, A. B. Brower
Henry Felson, Cincinnati	Julien E. Benjamin, H. B. Weiss, A. B. Brower
Roby John Flint Renshaw, Cleveland	Russell L. Haden, John Tucker, A. B. Brower
Walter Maximilian Solomon, Cleveland	John A. Toomey, Robert M. Stecher, A. B. Brower
John Walter Martin, Jr., Cleveland Heights	J. C. Placak, J. M. Hayman, A. B. Brower
Maurice Arthur Schnitker, Toledo	Samuel A. Levine, Soma Weiss, A. B. Brower
Oregon	
DeWitt Clinton Burkes, Portland	T. Homer Coffen, John H. Fitzgibbon, Homer P. Rush
Pennsylvania	
Henry Abraham Rothrock, Jr., Bethlehem	L. I. Fisher, Francis J. Dever, Edward L. Bortz
Oscar Thompson Wood, Jr., Bywood	Charles L. Brown, Thomas M. Durant, Edward L. Bortz
Dale C. Stahle, Harrisburg	C. E. Ervin, C. P. Faller, Edward L. Bortz
Charles Alexander Jones, Philadelphia	H. L. Bockus, H. Leon Jameson, Edward L. Bortz
George Lorenz, Jr., Philadelphia	Frank Walton Burge, B. B. Vincent Lyon, Edward L. Bortz
Robert Ivan Baxmeier, Pittsburgh	C. Howard Marcy, H. G. Schleiter, R. R. Snowden
Verner Bickart Callomon, Pittsburgh	Clifford C. Hartman, Ernest W. Willetts, R. R. Snowden
L. Lewis Pennock, Pittsburgh	Joseph H. Barach, Clement R. Jones, R. R. Snowden
George Gaius Shoemaker, Pittsburgh	C. Howard Marcy, Frank A. Evans, R. R. Snowden

Associateship Candidates	*Sponsors*
RHODE ISLAND	
Kalei Kaonohi Gregory, Providence	Herman A. Lawson, Francis H. Chafee, Alex. M. Burgess
Hugh Edward Kiene, Providence	Charles F. Gormly, Louis I. Kramer, Alex. M. Burgess
Edward Joseph West, Providence	Herman A. Lawson, Louis I. Kramer, Alex. M. Burgess
SOUTH CAROLINA	
Douglas Barnes Remsen, Charleston	Joseph H. Cannon, Francis B. Johnson, Kenneth M. Lynch
TENNESSEE	
John Davis Hughes, Memphis	Conley H. Sanford, Hugh F. Crawford, J. O. Manier
TEXAS	
David McMillan Marcley, Amarillo	George M. Cultra, Howard M. Odel, M. D. Levy
F. Peel Allison, Beaumont	L. T. Pruit, Titus H. Harris, M. D. Levy
William Hartsel Bradford, Dallas	C. Frank Brown, Milford O. Rouse, M. D. Levy
John Jose Andujar, Fort Worth	C. O. Terrell, Will S. Horn, M. D. Levy
Stephen Alexander Foote, Jr., Houston	John A. Alvarez, Paul V. Ledbetter, M. D. Levy
Sidney Schnur, Houston	Alvis E. Greer, H. N. Gemoets, M. D. Levy
Elmer Haynes, Rusk	Louis H. Bauer, Roy D. Grimmer, M. D. Levy
Harry Perry Thomas, Rusk	Robert G. McCorkle, Edgar M. McPeak, M. D. Levy
Joseph George Rushton, San Angelo	Frank H. Krusen, Russell M. Wilder, E. V. Allen, M. D. Levy
Henry Nathan Leopold, San Antonio	David R. Sacks, Lee Rice, M. D. Levy
UTAH	
James Clem Hayward, Logan	G. G. Richards, Fuller B. Bailey, T. A. Clawson, Jr., L. E. Viko
VIRGINIA	
Joseph Rogers Blalock, Marion	R. Finley Gayle, Jr., J. Morrison Hutcheson, Walter B. Martin
J. Franklin Waddill, Norfolk	A. B. Hodges, Wm. B. Newcomb, Walter B. Martin
M. Richard Whitehill, Norfolk	A. B. Hodges, Wm. B. Newcomb, Walter B. Martin
Edward Arthur Delarue, Jr., Richmond	Douglas G. Chapman, William B. Porter, Walter B. Martin
Clavel Tyrus Wilfong, Roanoke	Dean B. Cole, R. Finley Gayle, Jr., Walter B. Martin
WASHINGTON	
Frank George LeFor, Yakima	Howard L. Hull, Paul J. Lewis, C. E. Watts
WISCONSIN	
Arthur Andrews Holbrook, Milwaukee	William S. Middleton, Francis D. Murphy, Elmer L. Sevringhaus
DOMINION OF CANADA	
Ontario	
Joseph Leonard Duffy, London	Roderick J. Gordon, Frank S. Kennedy, J. H. Holbrook
MEXICO	
George Nelson Furbeck, Mexico	J. H. Musser, F. P. Miranda, James F. Churchill

OBITUARY

DR. FREDERICK J. COX

Dr. Frederick J. Cox, F.A.C.P., of Gilbertsville, N. Y., died on December 5, 1940, at the Flower Hospital in New York City. Dr. Cox was born in Albany, N. Y., June 28, 1866. He received his A.B. degree from Williams College in 1889 and graduated from the Albany Medical College in 1892. From 1895 to 1912, he was visiting physician to the Homeopathic Hospital of Albany, and in 1912 became the chief of the medical service of this hospital. During the World War, Dr. Cox served as Assistant Chief of the Medical Service, Base Hospital, Camp Upton, L. I., N. Y., and he attained the rank of Major in the Medical Corps of the U. S. Army. In his earlier career, he pursued postgraduate training at the École de Medicine in Paris, France, and later at the Harvard Medical School, Boston. He was a member of the American Institute of Homeopathy, the Homeopathic Medical Society of the State of New York, the Albany County Medical Society and the American Medical Association. He was a member of the American Congress on Internal Medicine and in 1923 was elected to Fellowship in the American College of Physicians.

CHARLES F. TENNEY, M.D., F.A.C.P.,
Governor for Eastern New York

ERRATUM

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